WEST

Freeform Search

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Term: wt-1 and peptid$4 and CD34

Display: 10 **Documents in Display Format:** CIT **Starting with Number** 1

Generate: ○ **Hit List** ◉ **Hit Count** ○ **Image**

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Search History

Today's Date: 10/24/2001

DB Name	Query	Hit Count	Set Name
USPT,PGPB,JPAB,EPAB,DWPI	wt-1 and peptid$4 and CD34	11	L10
USPT,PGPB,JPAB,EPAB,DWPI	(gao) AND (stauss)	1	L9
DWPI	(gao)[IN] AND (stauss)[IN]	1	L8
DWPI	l4 and gao	0	L7
DWPI	l4 and gau	0	L6
DWPI	(Wo000026249)	0	L5
DWPI	(0026249)	45	L4
DWPI	(0026249)[PFAP]	0	L3
DWPI	(9903572)[PFAP]	1	L2
DWPI	(0003572)[PFAP]	0	L1

WEST

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Search Results - Record(s) 1 through 10 of 11 returned.

☐ 1. Document ID: US 6261535 B1

L10: Entry 1 of 11 File: USPT Jul 17, 2001

US-PAT-NO: 6261535
DOCUMENT-IDENTIFIER: US 6261535 B1

TITLE: Diagnostic methods for targeting the vasculature of solid tumors

DATE-ISSUED: July 17, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thorpe; Philip E.	Dallas	TX		
Burrows; Francis J.	San Diego	CA		

US-CL-CURRENT: 424/1.49; 424/130.1, 424/133.1, 424/142.1, 424/145.1, 424/155.1, 424/156.1, 424/178.1, 424/179.1, 424/181.1, 424/183.1, 424/186.1, 424/9.32, 424/9.323, 424/9.34, 424/9.341, 424/9.36, 424/9.42, 530/387.1 , 530/388.1, 530/388.15, 530/388.22, 530/391.3, 530/391.7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6190661 B1

L10: Entry 2 of 11 File: USPT Feb 20, 2001

US-PAT-NO: 6190661
DOCUMENT-IDENTIFIER: US 6190661 B1

TITLE: Methods and compositions for the use of apurinic/apyrimidinic endonucleases

DATE-ISSUED: February 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kelley; Mark R.	Zionsville	IN		
Duquid; John	Brownsburg	IN		
Eble; John	Indianapolis	IN		

US-CL-CURRENT: 424/139.1; 436/63, 436/64, 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 6070126 A

L10: Entry 3 of 11 File: USPT May 30, 2000

US-PAT-NO: 6070126
DOCUMENT-IDENTIFIER: US 6070126 A

TITLE: Immunobiologically-active linear peptides and method of identification

DATE-ISSUED: May 30, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kokolus; William J.	Kenmore	NY	14217	
Fritsche; Herbert A.	Houston	TX		
Johnston; Dennis A.	Houston	TX		

US-CL-CURRENT: 702/19; 530/300

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

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☐ 4. Document ID: US 6051230 A

L10: Entry 4 of 11 File: USPT Apr 18, 2000

US-PAT-NO: 6051230
DOCUMENT-IDENTIFIER: US 6051230 A

TITLE: Compositions for targeting the vasculature of solid tumors

DATE-ISSUED: April 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thorpe; Philip E.	Dallas	TX		
Burrows; Francis J.	San Diego	CA		

US-CL-CURRENT: 424/178.1; 424/179.1, 424/180.1, 424/181.1, 424/182.1, 424/183.1, 530/387.1, 530/387.7, 530/388.1, 530/388.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

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☐ 5. Document ID: US 5965132 A

L10: Entry 5 of 11 File: USPT Oct 12, 1999

US-PAT-NO: 5965132
DOCUMENT-IDENTIFIER: US 5965132 A

TITLE: Methods and compositions for targeting the vasculature of solid tumors

DATE-ISSUED: October 12, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thorpe; Philip E.	Dallas	TX		
Burrows; Francis J.	San Diego	CA		

US-CL-CURRENT: 424/1.49; 424/1.45, 424/139.1, 424/156.1, 424/183.1, 435/70.1, 435/70.2, 530/387.2, 530/391.7, 530/391.9 , 530/807, 530/828

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 5919643 A

L10: Entry 6 of 11 File: USPT Jul 6, 1999

US-PAT-NO: 5919643
DOCUMENT-IDENTIFIER: US 5919643 A

TITLE: Methods and compositions for the use of apurinic/apyrimidinic endonucleases

DATE-ISSUED: July 6, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kelley; Mark R.	Zionsville	IN		
Duguid; John	Brownsburg	IN		
Eble; John	Indianapolis	IN		

US-CL-CURRENT: 435/19; 435/199

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 7. Document ID: US 5863538 A

L10: Entry 7 of 11 File: USPT Jan 26, 1999

US-PAT-NO: 5863538
DOCUMENT-IDENTIFIER: US 5863538 A

TITLE: Compositions for targeting the vasculature of solid tumors

DATE-ISSUED: January 26, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thorpe; Philip E.	Dallas	TX		
Burrows; Francis J.	San Diego	CA		

US-CL-CURRENT: 424/136.1; 424/138.1, 424/141.1, 424/154.1, 424/155.1, 424/172.1, 424/173.1, 424/174.1, 424/181.1, 530/387.3, 530/387.7, 530/388.22

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 8. Document ID: US 5855866 A

L10: Entry 8 of 11 File: USPT Jan 5, 1999

US-PAT-NO: 5855866
DOCUMENT-IDENTIFIER: US 5855866 A

TITLE: Methods for treating the vasculature of solid tumors

DATE-ISSUED: January 5, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thorpe; Philip E.	Dallas	TX		
Burrows; Francis J.	Dallas	TX		

US-CL-CURRENT: 424/1.49; 424/142.1, 424/155.1, 424/156.1, 424/178.1, 424/181.1, 424/183.1, 530/387.1, 530/388.15, 530/388.22, 530/388.8, 530/391.3, 530/391.7, 530/391.9

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 9. Document ID: US 5807978 A

L10: Entry 9 of 11 File: USPT Sep 15, 1998

US-PAT-NO: 5807978
DOCUMENT-IDENTIFIER: US 5807978 A

TITLE: Immunogenic peptides of prostate specific antigen

DATE-ISSUED: September 15, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kokolus; William J.	Houston	TX	77054	
Fritsche; Herbert A.	Houston	TX	77041	
Johnston; Dennis A.	Houston	TX	77062	

US-CL-CURRENT: 530/300; 424/184.1, 424/185.1, 424/277.1, 530/326, 530/327, 530/403

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 10. Document ID: US 5776427 A

L10: Entry 10 of 11 File: USPT Jul 7, 1998

US-PAT-NO: 5776427
DOCUMENT-IDENTIFIER: US 5776427 A

TITLE: Methods for targeting the vasculature of solid tumors

DATE-ISSUED: July 7, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thorpe; Philip E.	Dallas	TX		
Burrows; Francis J.	San Diego	CA		

US-CL-CURRENT: 424/1.49; 424/138.1, 424/143.1, 424/145.1, 424/178.1, 424/179.1, 424/181.1, 424/183.1, 424/93.21, 530/387.2, 530/388.2, 530/388.73, 530/391.7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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Generate Collection

Terms	Documents
wt-1 and peptid$4 and CD34	11

Display 10 Documents, starting with Document: 11

Display Format: CIT Change Format

WEST

Generate Collection

Search Results - Record(s) 11 through 11 of 11 returned.

☐ 11. Document ID: US 5660827 A

L10: Entry 11 of 11 File: USPT Aug 26, 1997

US-PAT-NO: 5660827
DOCUMENT-IDENTIFIER: US 5660827 A

TITLE: Antibodies that bind to endoglin

DATE-ISSUED: August 26, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thorpe; Philip E.	Dallas	TX		
Burrows; Francis J.	San Diego	CA		

US-CL-CURRENT: 424/152.1; 424/130.1, 424/138.1, 424/141.1, 530/387.1, 530/388.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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Terms	Documents
wt-1 and peptid$4 and CD34	11

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Display Format: CIT Change Format

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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Dec 17  The CA Lexicon available in the CAPLUS and CA files
 NEWS  3  Feb 06  Engineering Information Encompass files have new names
 NEWS  4  Feb 16  TOXLINE no longer being updated
 NEWS  5  Apr 23  Search Derwent WPINDEX by chemical structure
 NEWS  6  Apr 23  PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
 NEWS  7  May 07  DGENE Reload
 NEWS  8  Jun 20  Published patent applications (A1) are now in USPATFULL
 NEWS  9  JUL 13  New SDI alert frequency now available in Derwent's
                  DWPI and DPCI
 NEWS 10  Aug 23  In-process records and more frequent updates now in
                  MEDLINE
 NEWS 11  Aug 23  PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
 NEWS 12  Aug 23  Adis Newsletters (ADISNEWS) now available on STN
 NEWS 13  Sep 17  IMSworld Pharmaceutical Company Directory name change
                  to PHARMASEARCH
 NEWS 14  Oct 09  Korean abstracts now included in Derwent World Patents
                  Index
 NEWS 15  Oct 09  Number of Derwent World Patents Index updates increased
 NEWS 16  Oct 15  Calculated properties now in the REGISTRY/ZREGISTRY File
 NEWS 17  Oct 22  Over 1 million reactions added to CASREACT
 NEWS 18  Oct 22  DGENE GETSIM has been improved

 NEWS EXPRESS  August 15 CURRENT WINDOWS VERSION IS V6.0c,
               CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP),
               AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.15       0.15

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=> s wt-1 or (wilms)
L1       24221 WT-1 OR (WILMS)

=> s WT-1
L2       10173 WT-1

=> s l2 (P) CD34
L3           9 L2 (P) CD34

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4             3 DUP REM L3 (6 DUPLICATES REMOVED)

=> dis l4 1-3 ibib abs kwic

L4   ANSWER 1 OF 3     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:    2001093194     MEDLINE
DOCUMENT NUMBER:     20582378   PubMed ID: 11146163
TITLE:               Simultaneous expression of different immunogenic antigens
                     in acute myeloid leukemia.
AUTHOR:              Greiner J; Ringhoffer M; Simikopinko O; Szmaragowska A;
                     Huebsch S; Maurer U; Bergmann L; Schmitt M
CORPORATE SOURCE:    Third Department of Medicine, University of Ulm, Ulm,
                     Germany.
SOURCE:              EXPERIMENTAL HEMATOLOGY, (2000 Dec) 28 (12) 1413-22.
                     Journal code: EPR. ISSN: 0301-472X.
PUB. COUNTRY:        Netherlands
                     Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200101
ENTRY DATE:          Entered STN: 20010322
                     Last Updated on STN: 20010322
                     Entered Medline: 20010125
```

AB Identification of immunogenic leukemia-associated antigens as target structures is mandatory for specific immunotherapy of leukemia. Here, we define acute myeloid leukemia (AML) antigens eliciting a humoral immune response in the autologous host.We applied the method of serologic screening of cDNA expression libraries with autologous serum (SEREX). To date, this technique has been used to characterize antigen structures in solid tumors. The mRNA expression pattern of these newly in AML isolated antigens and previously described leukemia antigens (PRAME, MAGE-1, and Wt-1) was evaluated by reverse transcriptase polymerase chain reaction. For Wt-1, Western blotting also was performed.Screening of a cDNA expression library prepared from a patient with AML FAB M2 using autologous and allogeneic sera, followed by sequencing of positive clones, yielded three autoantigens (Prp1p/Zer1p, L19H1, and one without homology to previously described genes) and two antigens reactive with allogeneic sera (MAZ, PINCH). PRAME mRNA was expressed in 47% of 34 AML patients, but not in 13 CD34(+) cell samples or in peripheral blood mononuclear cells of 13 healthy volunteers. mRNA expression of MAZ was detected in 44% of AML patients, but only in 8% of healthy donors. Humoral responses to MAZ were detected in 35%. More than 80% of the screened AML patients showed simultaneous expression of two or more of these antigens.Differential expression in AML patients vs healthy volunteers suggests that the immunogenic antigens PRAME and MAZ are potential candidates for immunotherapy in AML.

AB . . . tumors. The mRNA expression pattern of these newly in AML isolated antigens and previously described leukemia antigens (PRAME, MAGE-1, and Wt-1) was evaluated by reverse transcriptase polymerase chain reaction. For Wt-1, Western blotting also was performed.Screening of a cDNA expression library prepared from a patient with AML FAB M2 using autologous. . . reactive with allogeneic sera (MAZ, PINCH). PRAME mRNA was expressed in 47% of 34 AML patients, but not in 13 CD34(+) cell samples or in peripheral blood mononuclear cells of 13 healthy volunteers. mRNA expression of MAZ was detected in 44%. . .

L4 ANSWER 2 OF 3 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97324127 MEDLINE
DOCUMENT NUMBER: 97324127 PubMed ID: 9180296
TITLE: Establishment and characterization of a new, factor-independent acute myeloid leukemia line designated Ei501.
AUTHOR: Weidmann E; Brieger J; Karakas T; Maurer U; Pascheberg U; Hoelzer D; Mitrou P S; Bergmann L
CORPORATE SOURCE: Medical Clinic III, Department of Internal Medicine, University Hospital, Johann-Wolfgang Goethe University, Frankfurt/M, Germany.
SOURCE: LEUKEMIA, (1997 May) 11 (5) 709-13.
Journal code: LEU; 8704895. ISSN: 0887-6924.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970709
Last Updated on STN: 19970709
Entered Medline: 19970626

AB We established a factor-independent acute myeloid leukemia cell line, designated Ei501. The line has been growing in RPMI 1640 media for 18 months and can be maintained without addition of growth factors. Ei501 is positive for myeloperoxidase and negative for esterase and PAS. Cytogenetic analysis revealed the FAB M3 associated t(15;17) translocation and a translocation of the chromosomes 7 and 8: 46 XX, -7, +t(7;8)(q32;q13), t(15;17)(q22;q12). This karyotype was confirmed by fluorescence in situ hybridization. Ei501 cells express AML-associated surface markers such as CD13, CD33 and CD38. Although 42% of the patient's blast cells were CD34-positive, the line lacks surface expression of CD34. Furthermore the line has a number of characteristics which are detectable in blasts from AML patients, such as surface adhesion molecules, cytokines such as TGF-beta, cytokine receptors such as the IL-2 receptor beta and gamma chains or the IL-4 receptor and the genes for the transcription factor wt-1 (Wilms' tumor gene) and for the proto-oncogene bcl-2, both shown to be present in the majority of patients with AML. Additionally the line can be used as target in cytotoxicity assays using IL-2 activated cytotoxic lymphocytes as effector cells. In conclusion, besides a rare karyotype the Ei501 cell line has several features common in AML, and may therefore be used as a model to study pathogenetic mechanisms in acute myeloid leukemia.

AB . . . Ei501 cells express AML-associated surface markers such as CD13, CD33 and CD38. Although 42% of the patient's blast cells were CD34 -positive, the line lacks surface expression of CD34. Furthermore the line has a number of characteristics which are detectable in blasts from AML patients, such as surface adhesion. . . such as the IL-2 receptor beta and gamma chains or the IL-4 receptor and the genes for the transcription factor wt-1 (Wilms' tumor gene) and for the proto-oncogene bcl-2, both shown to be present in the majority of patients with AML.. . .

L4 ANSWER 3 OF 3 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 96119558 MEDLINE
DOCUMENT NUMBER: 96119558 PubMed ID: 8589020
TITLE: The Wilms' tumor gene is frequently expressed in acute myeloblastic leukemias and may provide a marker for residual blast cells detectable by PCR.
AUTHOR: Brieger J; Weidmann E; Maurer U; Hoelzer D; Mitrou P S; Bergmann L
CORPORATE SOURCE: Medical Clinic III, Hematology-Oncology, J. W. Goethe University, Frankfurt/M., Germany.
SOURCE: ANNALS OF ONCOLOGY, (1995 Oct) 6 (8) 811-6.
Journal code: AYF; 9007735. ISSN: 0923-7534.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960404
Last Updated on STN: 20000303
Entered Medline: 19960327

AB BACKGROUND: The tumor suppressor gene wt-1 was isolated by cytogenetic deletion analysis of patients with Wilms' tumor (wt-1). This gene encodes for a zinc finger DNA-binding protein with transcription-repressing properties. During normal ontogenesis it is expressed in a time- and tissue-dependent manner mainly in the kidneys and gonads. Recently, the expression of wt-1 in acute leukemias (AL) was reported. Here we investigated the

prognostic potential of wt-1 mRNA expression during
the course of the disease using the PCR technique. PATIENTS AND METHODS:
Blast cells from 83 patients with newly diagnosed AML and 20 AML patients
during follow-up in complete remission were analyzed for wt-
1 mRNA expression. Peripheral blood mononuclear cells (PBMNC) and
bone marrow (BM) from healthy persons (n = 13) and sorted CD34
-positive cells from normal donors (n = 4) were used as negative controls.
RESULTS: Wt-1-specific m-RNA was detectable in 67/83
(81%) patients with AML. Normal donors did not express wt-
1 m-RNA but in 1/4 sorted CD34+ cell samples a weak
amplified product was observed. After achieving cytological CR 14/20
studied patients lost wt-1 expression. In 7/8 patients
in morphological CR the reappearance of wt-1
expression preceded relapse of the disease, in 1/8 patients wt-
1 remained positive in CR. Response to therapy, disease-free
survival, overall survival and FAB-subtype did not correlate with
wt-1 m-RNA expression in newly diagnosed AML before
therapy. CONCLUSIONS: In the majority of acute leukemias wt-
1 is expressed and probably blast cell-associated, at least in
levels detectable by PCR. Wt-1 mRNA was detectable in
bone marrow cells of AML patients in clinical CR. The results strongly
suggest that the persistence or reappearance of wt-1
predicts relapse of the disease prior to morphological relapse.
AB BACKGROUND: The tumor suppressor gene wt-1 was
isolated by cytogenetic deletion analysis of patients with Wilms' tumor (
wt-1). This gene encodes for a zinc finger DNA-binding
protein with transcription-repressing properties. During normal
ontogenesis it is expressed in a time- and tissue-dependent manner mainly
in the kidneys and gonads. Recently, the expression of wt-
1 in acute leukemias (AL) was reported. Here we investigated the
prognostic potential of wt-1 mRNA expression during
the course of the disease using the PCR technique. PATIENTS AND METHODS:
Blast cells from 83 patients with newly diagnosed AML and 20 AML patients
during follow-up in complete remission were analyzed for wt-
1 mRNA expression. Peripheral blood mononuclear cells (PBMNC) and
bone marrow (BM) from healthy persons (n = 13) and sorted CD34
-positive cells from normal donors (n = 4) were used as negative controls.
RESULTS: Wt-1-specific m-RNA was detectable in 67/83
(81%) patients with AML. Normal donors did not express wt-
1 m-RNA but in 1/4 sorted CD34+ cell samples a weak
amplified product was observed. After achieving cytological CR 14/20
studied patients lost wt-1 expression. In 7/8 patients
in morphological CR the reappearance of wt-1
expression preceded relapse of the disease, in 1/8 patients wt-
1 remained positive in CR. Response to therapy, disease-free
survival, overall survival and FAB-subtype did not correlate with
wt-1 m-RNA expression in newly diagnosed AML before
therapy. CONCLUSIONS: In the majority of acute leukemias wt-
1 is expressed and probably blast cell-associated, at least in
levels detectable by PCR. Wt-1 mRNA was detectable in
bone marrow cells of AML patients in clinical CR. The results strongly
suggest that the persistence or reappearance of wt-1
predicts relapse of the disease prior to morphological relapse.

```
=> dis his

     (FILE 'HOME' ENTERED AT 19:59:20 ON 24 OCT 2001)

     FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 19:59:31 ON 24 OCT 2001
L1        24221 S WT-1 OR (WILMS)
L2        10173 S WT-1
L3            9 S L2 (P) CD34
L4            3 DUP REM L3 (6 DUPLICATES REMOVED)

=> s l2 (P) (cancer or leukemia or CML or AML)
L5          147 L2 (P) (CANCER OR LEUKEMIA OR CML OR AML)

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6          100 DUP REM L5 (47 DUPLICATES REMOVED)

=> s l6 (P) peptid
<------User Break------>

=> s l6 (P) peptide?
L7            5 L6 (P) PEPTIDE?

=> dis l7 1-5 ibib abs kwic

L7   ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2000:314730  CAPLUS
DOCUMENT NUMBER:          132:333396
TITLE:                    Immunotherapy of cancer using epitopes of WT-1 and
                          GATA-1 transcription factors
INVENTOR(S):              Stauss, Hans Josef; Gao, Liquan
PATENT ASSIGNEE(S):       Imperial College Innovations Limited, UK
SOURCE:                   PCT Int. Appl., 93 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 2000026249      A1   20000511       WO 1999-GB3572   19991102
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
             CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
             IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
             MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
             SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9964797         A1   20000522       AU 1999-64797    19991102
     EP 1127068         A1   20010829       EP 1999-952682   19991102
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
PRIORITY APPLN. INFO.:                    GB 1998-23897    A  19981102
                                          WO 1999-GB3572   W  19991102
AB   The authors disclose that the peptides RMFPNAPYL or CMTWNQMNL
```

are epitopes for cytotoxic T-cells recog[redacted]g **WT-1** in an HLA-A2-restricted manner. In addn. the **peptide** is HLMPFPGPLL is a CTL epitope of human GATA-1 transcription factor. The **peptides**, and polynucleotides encoding them, may be useful as **cancer** vaccines.
REFERENCE COUNT: 3
REFERENCE(S): (1) Anon; J BIOL CHEM
(2) Massachusetts Inst Technology; WO 9107509 A 1991 CAPLUS
(3) Wistar Inst; WO 9529995 A 1995 CAPLUS
AB The authors disclose that the **peptides** RMFPNAPYL or CMTWNQMNL are epitopes for cytotoxic T-cells recognizing **WT-1** in an HLA-A2-restricted manner. In addn. the **peptide** is HLMPFPGPLL is a CTL epitope of human GATA-1 transcription factor. The **peptides**, and polynucleotides encoding them, may be useful as **cancer** vaccines.
IT **Peptides**, biological studies
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(of **WT-1** and GATA-1 transcription factors for immunotherapy of **cancer**)
IT **Peptides**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(retro-inverso; for epitopes of GATA-1 and **WT-1** transcription factors in relation to immunotherapy of **cancer**)

L7 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:341423 CAPLUS
DOCUMENT NUMBER: 122:129828
TITLE: Phenotypic changes induced in small cell lung carcinoma cells by overexpression of myc and ras oncogenes
AUTHOR(S): Buerger, Christiane; Scheffler, Sonja; Elsasser, Hans-Peter; Adamkiewicz, Juergen
CORPORATE SOURCE: Institut Molekularbiologie und Tumorforschung, Philipps-Universitaet, Marburg, D-35037, Germany
SOURCE: Mol. Cell. Differ. (1994), 2(4), 373-98
CODEN: MCDIEL; ISSN: 1065-3074
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Overexpression of c-myc and activated H-ras oncogenes in the small-cell lung carcinoma (SCLC) cell lines NCI-N592 and NCI-H69 caused characteristic phenotypic changes in these cells, supporting the hypothesis that a transition from an SCLC to an non-small-cell lung carcinoma (NSCLC) large-cell carcinoma phenotype was induced. To obtain more detailed information about this process, the authors compared in c-myc- and activated H-ras-transfected cells and in the corresponding parental cells the expression or activity of both new and established lung **cancer** cell type-specific markers. The transfected cells lost SCLC-specific TRE-binding activity detectable in electrophoretic mobility shift assays and showed a higher expression of the tumor suppressor genes Rb-1 and **Wt-1** characteristic for NSCLC cell lines. Furthermore, they expressed an NSCLC large-cell undifferentiated lung carcinoma cell-specific OTF-2/Oct-2 RNA. The expression of most known SCLC-specific marker genes remained unchanged, which is in agreement with the frequent detection of neuroendocrine markers in large-cell carcinomas. However, the gene encoding gastrin-releasing **peptide** was down regulated in the transfected cells. Most of these changes were detectable in transfected cells in vitro as well as in nude mouse tumors, thus excluding cell culture artifacts. Apparently, the authors have identified early markers of a cell type transition pathway that might help to define an initial phase in the progression toward a treatment-resistant tumor state occurring in more than 90% of SCLCs.
AB Overexpression of c-myc and activated H-ras oncogenes in the small-cell lung carcinoma (SCLC) cell lines NCI-N592 and NCI-H69 caused characteristic phenotypic changes in these cells, supporting the hypothesis that a transition from an SCLC to an non-small-cell lung carcinoma (NSCLC) large-cell carcinoma phenotype was induced. To obtain more detailed information about this process, the authors compared in c-myc- and activated H-ras-transfected cells and in the corresponding parental cells the expression or activity of both new and established lung **cancer** cell type-specific markers. The transfected cells lost SCLC-specific TRE-binding activity detectable in electrophoretic mobility shift assays and showed a higher expression of the tumor suppressor genes Rb-1 and **Wt-1** characteristic for NSCLC cell lines. Furthermore, they expressed an NSCLC large-cell undifferentiated lung carcinoma cell-specific OTF-2/Oct-2 RNA. The expression of most known SCLC-specific marker genes remained unchanged, which is in agreement with the frequent detection of neuroendocrine markers in large-cell carcinomas. However, the gene encoding gastrin-releasing **peptide** was down regulated in the transfected cells. Most of these changes were detectable in transfected cells in vitro as well as in nude mouse tumors, thus excluding cell culture artifacts. Apparently, the authors have identified early markers of a cell type transition pathway that might help to define an initial phase in the progression toward a treatment-resistant tumor state occurring in more than 90% of SCLCs.

L7 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:503357 CAPLUS
DOCUMENT NUMBER: 103:103357
TITLE: Preparation of antibodies to human leukemia virus
PATENT ASSIGNEE(S): Japanese Foundation for Cancer Research, Japan; Otsuka Pharmaceutical Co., Ltd.
SOURCE: Jpn. Kokai Tokkyo Koho, 20 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 60067432	A2	19850417	JP 1983-176079	19830922
JP 04079356	B4	19921215		

AB Antibodies to human **leukemia** virus are isolated from blood serum of mammals immunized by complexes consisting of human **leukemia** virus-related **peptides** and carriers. Thus, a procedure is described for the prepn. of H-Tyr-Val-Glu-Pro-Thr-Ala-Pro-Gln-Val-Leu-OH. An immune antigen is prepd. by forming complexes of the **peptide** with Ascaris exts. (av. mol. **wt.** 1 .times. 105) used as carriers. The antigen is administered to rabbits, and the antibodies are isolated from the serum.
AB Antibodies to human **leukemia** virus are isolated from blood serum

of mammals immunized by complexes consist[redacted] of human **leukemia** virus-related **peptides** and carriers. Thus, a procedure is described for the prepn. of H-Tyr-Val-Glu-Pro-Thr-Ala-Pro-Gln-Val-Leu-OH. An immune antigen is prepd. by forming complexes of the **peptide** with Ascaris exts. (av. mol. **wt.** 1 .times. 105) used as carriers. The antigen is administered to rabbits, and the antibodies are isolated from the serum.

L7 ANSWER 4 OF 5 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:293494 BIOSIS
DOCUMENT NUMBER: PREV200100293494
TITLE: Immunoresponse to Wilms tumor antigen-1 (WT-1) in CML patients.
AUTHOR(S): Bellantuono, Ilaria (1); Macchiarulo, Eugenio (1); Gao, Liquan (1); Dazzi, Francesco; Cerundolo, Vincenzo; Marley, Stephen B.; Gordon, Myrtle Y.; Goldman, John M.; Stauss, Hans J. (1)
CORPORATE SOURCE: (1) Immunology, ICSM Hammersmith Hospital, London UK
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 144a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology . ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have previously characterised the **WT-1** HLA-A2.1 restricted **peptide** epitope p126-134 and shown that allorestricted CTLs recognising specifically the p126-134 epitope were able efficiently and selectively to lyse **CML** progenitor cells. The aim of the present study is to investigate whether an immunoresponse to the **WT-1** p126 epitope is present in **CML** patients. Tetramers specific for the p126 **peptide** epitope were used to quantify the frequency of **WT-1** specific CD8 T cells ex vivo from freshly separated PBMC of **CML** patients and normal donors. CTL cell lines raised against the p126 **peptides** stained brightly with the fluorescent p126 tetramers and no staining was seen when irrelevant tetramers were used instead. This indicates that the tetrameric complexes selectively stain **WT-1** p126 specific CTLs. **CML** patients and normal donors were selected for the study on the basis of the expression of the HLA-A2.1 allele. PBMC from 10 HLA-A2.1 positive **CML** patients (4 IFN, 3 post-BMT, 2 post-DLI and 1 HU) and 7 HLA-A2 negative **CML** controls (4 HU, 2 post-BMT and 1 IFN) were triple stained with anti-CD8, anti-CD4 mAbs and with the p126 tetrameric complexes. In two out of 10 HLA-A2.1 positive **CML** cells 0.04% of CD8+ cells stained with the tetramer, equivalent to a frequency of 1:2500 CD8+ T cells. This exceeded the background level of 0.03% in circulating CD8+ cells observed in the control group of HLA-A2 negative **CML** patients and in HLA-A2 positive PBMC in normal donors (5 donors examined). The present tetramer data are compatible with a lack of CTL responses to the **WT-1** p126 epitope or with a low frequency of specific CTLs in **CML** patients. Ongoing functional experiments will show whether p126 responsive CTLs can be isolated from HLA-A2.1 positive **CML** patients. These experiments will determine whether the p126 epitope can be used for vaccination strategies aimed at expanding autologous CTLs, or whether strategies based on allo-restricted CTLs will be required to overcome poor autologous T cell responses.
AB We have previously characterised the **WT-1** HLA-A2.1 restricted **peptide** epitope p126-134 and shown that allorestricted CTLs recognising specifically the p126-134 epitope were able efficiently and selectively to lyse **CML** progenitor cells. The aim of the present study is to investigate whether an immunoresponse to the **WT-1** p126 epitope is present in **CML** patients. Tetramers specific for the p126 **peptide** epitope were used to quantify the frequency of **WT-1** specific CD8 T cells ex vivo from freshly separated PBMC of **CML** patients and normal donors. CTL cell lines raised against the p126 **peptides** stained brightly with the fluorescent p126 tetramers and no staining was seen when irrelevant tetramers were used instead. This indicates that the tetrameric complexes selectively stain **WT-1** p126 specific CTLs. **CML** patients and normal donors were selected for the study on the basis of the expression of the HLA-A2.1 allele. PBMC from 10 HLA-A2.1 positive **CML** patients (4 IFN, 3 post-BMT, 2 post-DLI and 1 HU) and 7 HLA-A2 negative **CML** controls (4 HU, 2 post-BMT and 1 IFN) were triple stained with anti-CD8, anti-CD4 mAbs and with the p126 tetrameric complexes. In two out of 10 HLA-A2.1 positive **CML** cells 0.04% of CD8+ cells stained with the tetramer, equivalent to a frequency of 1:2500 CD8+ T cells. This exceeded the background level of 0.03% in circulating CD8+ cells observed in the control group of HLA-A2 negative **CML** patients and in HLA-A2 positive PBMC in normal donors (5 donors examined). The present tetramer data are compatible with a lack of CTL responses to the **WT-1** p126 epitope or with a low frequency of specific CTLs in **CML** patients. Ongoing functional experiments will show whether p126 responsive CTLs can be isolated from HLA-A2.1 positive **CML** patients. These experiments will determine whether the p126 epitope can be used for vaccination strategies aimed at expanding autologous CTLs,. . .

L7 ANSWER 5 OF 5 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:94441 BIOSIS
DOCUMENT NUMBER: PREV200000094441
TITLE: HLA class I-restricted lysis of leukemia cells by a CD8+ cytotoxic T-lymphocyte clone specific for WT1 peptide.
AUTHOR(S): Ohminami, Hideki; Yasukawa, Masaki (1); Fujita, Shigeru
CORPORATE SOURCE: (1) First Department of Internal Medicine, Ehime University School of Medicine, Shigenobu, Ehime, 791-0295 Japan
SOURCE: Blood, (Jan. 1, 2000) Vol. 95, No. 1, pp. 286-293. ISSN: 0006-4971.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The Wilms tumor (WT1) gene has been reported to be preferentially expressed in acute leukemia cells, regardless of leukemia subtype and chronic myelogenous leukemia cells in blast crisis, but not in normal cells. This finding suggests strongly that WT1 protein is a potential target of immunotherapy for human leukemia. In this study, we established a CD8+ cytotoxic T-lymphocyte (CTL) clone directed against a WT1-derived peptide and examined its immunologic actions on leukemia cells. A CD8+ CTL clone, designated TAK-1, which lysed autologous cells loaded with a WT1-derived 9-mer peptide consisting of the HLA-A24 (HLA-A*2402)-binding motifs was established by stimulating CD8+ T lymphocytes from a healthy

individual repeatedly with WT1 peptide-pu[redacted] autologous dendritic cells. TAK-1 was cytotoxic to HLA-A24-positive le[redacted]emia cells expressing WT1, but not to HLA-A24-positive lymphoma cells that did not express WT1, HLA-A24-negative leukemia cells, or HLA-A24-positive normal cells. Treating leukemia cells with an antisense oligonucleotide complementary to the WT1 gene resulted in reduced TAK-1-mediated cytotoxicity, suggesting that target antigen of TAK-1 on leukemia cells is the naturally processed WT1 peptide in the context of HLA-A24. TAK-1 did not inhibit colony formation by normal bone marrow cells of HLA-A24-positive individuals. Because WT1 is overexpressed ubiquitously in various types of leukemia cells, but not in normal cells, immunotherapy using WT1 peptide-specific CTL clones should be an efficacious treatment for human leukemia.

IT Major Concepts
Tumor Biology

IT Parts, Structures, & Systems of Organisms
CD8-positive cytotoxic T-lymphocytes: HLA class I-restricted **leukemia** cell lysis, **WT-1 peptide** specific clone, blood and lymphatics, immune system

IT Diseases
leukemia: blood and lymphatic disease, immunotherapy, in-vitro cell study, neoplastic disease

=> s Stauss H?/au or Gao L?/au
L8 2596 STAUSS H?/AU OR GAO L?/AU

=> s l8 and wt-1
L9 3 L8 AND WT-1

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10 3 DUP REM L9 (0 DUPLICATES REMOVED)

=> dis l10 1-3 ibib abs

L10 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:314730 CAPLUS
DOCUMENT NUMBER: 132:333396
TITLE: Immunotherapy of cancer using epitopes of **WT-1** and GATA-1 transcription factors
INVENTOR(S): **Stauss, Hans Josef; Gao, Liquan**
PATENT ASSIGNEE(S): Imperial College Innovations Limited, UK
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000026249	A1	20000511	WO 1999-GB3572	19991102
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9964797	A1	20000522	AU 1999-64797	19991102
EP 1127068	A1	20010829	EP 1999-952682	19991102
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: GB 1998-23897 A 19981102
WO 1999-GB3572 W 19991102

AB The authors disclose that the peptides RMFPNAPYL or CMTWNQMNL are epitopes for cytotoxic T-cells recognizing **WT-1** in an HLA-A2-restricted manner. In addn. the peptide is HLMPFPGPLL is a CTL epitope of human GATA-1 transcription factor. The peptides, and polynucleotides encoding them, may be useful as cancer vaccines.

REFERENCE COUNT: 3
REFERENCE(S): (1) Anon; J BIOL CHEM
(2) Massachusetts Inst Technology; WO 9107509 A 1991 CAPLUS
(3) Wistar Inst; WO 9529995 A 1995 CAPLUS

L10 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:293494 BIOSIS
DOCUMENT NUMBER: PREV200100293494
TITLE: Immunoresponse to Wilms tumor antigen-1 (**WT-1**) in CML patients.
AUTHOR(S): Bellantuono, Ilaria (1); Macchiarulo, Eugenio (1); **Gao, Liquan (1)**; Dazzi, Francesco; Cerundolo, Vincenzo; Marley, Stephen B.; Gordon, Myrtle Y.; Goldman, John M.; **Stauss, Hans J. (1)**
CORPORATE SOURCE: (1) Immunology, ICSM Hammersmith Hospital, London UK
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 144a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We have previously characterised the **WT-1** HLA-A2.1 restricted peptide epitope p126-134 and shown that allorestricted CTLs recognising specifically the p126-134 epitope were able efficiently and selectively to lyse CML progenitor cells. The aim of the present study is to investigate whether an immunoresponse to the **WT-1** p126 epitope is present in CML patients. Tetramers specific for the p126 peptide epitope were used to quantify the frequency of **WT-1** specific CD8 T cells ex vivo from freshly separated PBMC of CML patients and normal donors. CTL cell lines raised against the p126 peptides stained brightly with the fluorescent p126 tetramers and no staining was seen when irrelevant tetramers were used instead. This indicates that the tetrameric complexes selectively stain **WT-1** p126 specific CTLs. CML patients and normal donors were selected for the study on the basis of the expression of the HLA-A2.1 allele. PBMC from 10 HLA-A2.1 positive CML patients (4 IFN, 3 post-BMT, 2 post-DLI and 1 HU) and 7 HLA-A2 negative CML controls (4 HU, 2 post-BMT and 1 IFN) were

triple stained with anti-CD8, anti-CD4 m[redacted]d with the p126 tetrameric complexes. In two out of 10 HLA-A2.1 positive CML cells 0.04% of CD8+ cells stained with the tetramer, equivalent to a frequency of 1:2500 CD8+ T cells. This exceeded the background level of 0.03% in circulating CD8+ cells observed in the control group of HLA-A2 negative CML patients and in HLA-A2 positive PBMC in normal donors (5 donors examined). The present tetramer data are compatible with a lack of CTL responses to the **WT-1** p126 epitope or with a low frequency of specific CTLs in CML patients. Ongoing functional experiments will show whether p126 responsive CTLs can be isolated from HLA-A2.1 positive CML patients. These experiments will determine whether the p126 epitope can be used for vaccination strategies aimed at expanding autologous CTLs, or whether strategies based on allo-restricted CTLs will be required to overcome poor autologous T cell responses.

L10 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:47026 BIOSIS
DOCUMENT NUMBER: PREV200000047026
TITLE: Selective elimination of leukemic progenitors by allorestricted CTL specific for Wilms tumor antigen-1 (**WT-1**.
AUTHOR(S): Bellantuono, I. (1); **Gao, L.**; Elsaesser, A.; Marley, S.; Gordon, M.; Goldman, J.; **Stauss, H.**
CORPORATE SOURCE: (1) Department of Immunology, Hammersmith Hospital, London UK
SOURCE: Blood, (Nov. 15, 1999) Vol. 94, No. 10 SUPPL. 1 PART 1, pp. 532a-533a.
Meeting Info.: Forty-first Annual Meeting of the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999 The American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

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☐ 1. Document ID: US 6261535 B1

L10: Entry 1 of 11 File: USPT Jul 17, 2001

US-PAT-NO: 6261535
DOCUMENT-IDENTIFIER: US 6261535 B1

TITLE: Diagnostic methods for targeting the vasculature of solid tumors

DATE-ISSUED: July 17, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thorpe; Philip E.	Dallas	TX		
Burrows; Francis J.	San Diego	CA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The University of Texas System Board of Regents	Austin	TX			02

APPL-NO: 9/ 207277
DATE FILED: December 8, 1998

PARENT-CASE:
The present application is a continuing application based upon application Ser. No. 08/350,212, filed Dec. 5, 1994 (now issued as U.S. Pat. No. 5,965,132), which is a continuation-in-part of U.S. patent application Ser. No. 08/205,330, filed Mar. 2, 1994 now U.S. Pat. No. 5,855,866; which is a continuation-in-part of U.S. patent application Ser. No. 07/846,349, filed Mar. 5, 1992. The entire text and figures of which disclosures are specifically incorporated by reference herein without disclaimer.

INT-CL: [7] A61K 51/10, A61K 39/395, C07K 16/00
US-CL-ISSUED: 424/1.49; 424/1.49, 424/9.32, 424/9.341, 424/9.36, 424/178.1, 424/179.1, 424/9.42, 424/186.1, 424/130.1, 424/133.1, 424/183.1, 424/142.1, 424/145.1, 424/181.1, 424/155.1, 424/9.34, 424/9.323, 424/156.1, 530/391.7, 530/391.3, 530/388.1, 530/388.15, 530/388.22, 530/387.1
US-CL-CURRENT: 424/1.49; 424/130.1, 424/133.1, 424/142.1, 424/145.1, 424/155.1, 424/156.1, 424/178.1, 424/179.1, 424/181.1, 424/183.1, 424/186.1, 424/9.32, 424/9.323, 424/9.34, 424/9.341, 424/9.36, 424/9.42, 530/387.1 , 530/388.1, 530/388.15, 530/388.22, 530/391.3, 530/391.7
FIELD-OF-SEARCH: 424/1.49, 424/178.1, 424/9.32, 424/9.341, 424/9.34, 424/9.323, 424/179.1, 424/156.1, 424/183.1, 424/142.1, 424/9.36, 424/9.42, 530/387.1, 530/388.1, 530/388.22, 530/388.15, 530/391.3

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4926869	May 1990	Rubin et al.	128/654
5191067	March 1993	Lappi et al.	530/399
5308622	May 1994	Casscells et al.	424/422
5354778	October 1994	Ray et al.	514/592
5576288	November 1996	Lappi et al.	514/2
5586297	December 1996	Jacobsone et al.	435/29
5660827	August 1997	Thorpe et al.	424/152.1
5677181	October 1997	Parish	435/332
5679637	October 1997	Lappi et al.	514/2
5776427	July 1998	Thorpe et al.	424/1.49
5855866	January 1999	Thorpe et al.	424/1.49
5863538	January 1999	Thorpe et al.	424/136.1
5874081	February 1999	Parish	424/130.1
5942602	August 1999	Wels et al.	530/388.22
5965132	October 1999	Thorpe et al.	424/149
6037329	March 2000	Baird et al.	514/44
6051230	April 2000	Thorpe et al.	424/178.1
6107090	August 2000	Bander	435/344
6129915	October 2000	Wels et al.	424/143.1
6136311	October 2000	Bander	424/155.1
6150508	November 2000	Murphy et al.	530/387.1

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 97/45544	December 1997	WOX	
WO 99/58570	November 1999	WOX	

OTHER PUBLICATIONS

Denekamp, J. Prog. appl. Microcirc. vol. 4, 28-38, 1984.*
Klagsbrun, Ann. Rev. Physiol, 53;217-239, 1990.*
Heimbrook et al., "Transforming growth factor .alpha.-Pseudomonas exotoxin fusion protein prolongs survival of nude mice bearing tumor xenografts," Proc. Natl. Acad. Sci. USA, 87:4697-4701, 1990.
Hirota et al., "Suppression of an epidermal growth factor receptor-hyperproducing tumor by an immunotoxin conjugate of gelonin and a monoclonal anti-epidermal growth factor receptor antibody," Cancer Research, 49:7106-7109, 1989.
International Search Report for WO99/58570 (PCT/EP99/03210), republished Mar. 16, 2000.

ART-UNIT: 169
PRIMARY-EXAMINER: Dudash; Diana
ASSISTANT-EXAMINER: Sharareh; Shahnam
ATTY-AGENT-FIRM: Williams, Morgan and Amerson

ABSTRACT:

The present invention relates generally to methods and compositions for targeting the vasculature of solid tumors using immunological- and growth factor-based reagents. In particular aspects, antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature of solid tumor masses through recognition of tumor vasculature-associated antigens, such as, for example, through endoglin binding, or through the specific induction of endothelial cell

surface antigens on vascular endothelial cells in solid tumors.

27 Claims, 37 Drawing figures

☐ 2. Document ID: US 6190661 B1

L10: Entry 2 of 11 File: USPT Feb 20, 2001

US-PAT-NO: 6190661
DOCUMENT-IDENTIFIER: US 6190661 B1

TITLE: Methods and compositions for the use of apurinic/apyrimidinic endonucleases

DATE-ISSUED: February 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kelley; Mark R.	Zionsville	IN		
Duquid; John	Brownsburg	IN		
Eble; John	Indianapolis	IN		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Advanced Research & Technology Institute	Bloomington	IN			02

APPL-NO: 9/ 336890
DATE FILED: June 18, 1999

PARENT-CASE:
This is a divisional of application Ser. No. 08/872,719, filed Jun. 11, 1997, now U.S. Pat. No. 5,919,643, which claims priority to provisional U.S. patent application Ser. Nos. 60/019,561, filed Jun. 11, 1996 and 60/019,602, filed June 11, 1996. The entire text of each of the above-referenced disclosures is specifically incorporated by reference herein without disclaimer.

INT-CL: [7] A61K 39/395, A61K 31/711
US-CL-ISSUED: 424/139.1; 514/44, 436/63, 436/64
US-CL-CURRENT: 424/139.1; 436/63, 436/64, 514/44
FIELD-OF-SEARCH: 514/44, 424/139.1, 436/63, 436/64

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4618585	October 1986	Chan	435/240
4633886	January 1987	Bucaro, Jr.	128/749
4666845	May 1987	Mattes et al.	435/240
4862899	September 1989	Bucaro	128/749
5171666	December 1992	Gutowski et al.	530/387.3
5306811	April 1994	Duffy	530/412
5320956	June 1994	Willingham et al.	435/172.2
5330972	July 1994	Coper	514/2
5360893	November 1994	Owens et al.	530/350
5399586	March 1995	Davies et al.	514/448

OTHER PUBLICATIONS

Bosari, S., et al. (1994) J. Natl. Can. Inst. 86(9), 681-687.
Demple, B., et al. (1991) Proc. Natl. Acad. Sci., USA 99, 11450-11454.
Duguid, J.R., et al. (1995) Can. Res. 55, 6097-6102.
Henner, W.D., et al. (1987) Nucl. Acids Res. 15(14), 5529-5544.
Hughes-Davies, I., et al. (1995) Int. J. Oncol. 6, 749-752.
Robertson, K.A., et al. (1997) Cell Growth Diff. 8, 443-449.
Xu, Y., et al. (1997) Antican. Res. 17, 1-7.
Ali et al., "Heterogeneity of subcellular localization of p53 protein in human glioblastomas," Cancer Res., 54:1-5, 1994.
Bamford, et al. "An immunohistochemical study of the distribution of epithelial antigens in the uterine cervix," Obstetrics & Gynecology, 61(5):603-608, 1983.
Battaglia et al., "Immunosuppressive acidic protein (IAP) and squamous cell carcinoma antigen (SCC) in patients with cervical cancer," Gynecol. Oncol., 53:176-182, 1994.
Bychkov et al., "Immunocytochemical localization of carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP) and Human chorionic gonadotropin (HCG) in cervical neoplasia," Am. J. Clin. Pathol., 79(4):414-420, 1983.
Duk et al., "Cancer of the uterine cervix: Sensitivity and specificity of serum squamous cell carcinoma antigen determinations," Gynecol. Oncol., 39:186-194, 1990.
Emanuele et al., "In vivo effect of ethanol on release of LH-releasing hormone and LH in rats," J. Endocrinol., 121:37-41, 1989.
Emanuele et al., "In vivo effects of acute EtOH on rat .alpha. and .beta. luteinizing hormone gene expression," Alcohol, 8:345-348, 1991.
Emanuele et al., "The effect of acute in vivo ethanol exposure on follicle stimulating hormone transcription and translation," Alcohol Clin. Exp. Res., 16(4):776-780, 1992.
Emanuele et al., "The effect of `binge` ethanol exposure on growth hormone and prolactin gene expression and secretion," Endocrinol., 131(5):2077-2082, 1992.
Gocze et al., "Serum levels of squamous cell carcinoma antigen and ovarian carcinoma antigen (CA 125) in patients with benign and malignant diseases of the uterine cervix," Oncol., 51:430-434, 1994.
Hale et al., "Prognostic value of epidermal growth factor receptor expression in cervical carcinoma," J. Clin. Pathol., 46:149-153, 1993.
International Search Report dated Nov. 11, 1997 (PCT/US97/10078) (INDY:012P).
Kainz et al., "Cytokeratin subunit 19 measured by CYFRA21-1 assay in follow-up of cervical cancer," Gynecol. Oncol., 56:402-405, 1995.
Kelley et al., "Cross-reaction of albumin with polyclonal LH antibody on western blots," Endo. Res., 16(4);477-491, 1990.
Lam et al., "Evaluation of carcinoembryonic antigen, tissue polypeptide antigen, and squamous cell carcinoma antigen in the detection of cervical cancers," Chinese Med. J., 50(1):7-13, 1992.
Lehtovirta et al., "Comparison between squamous cell carcinoma-associated antigen and CA-125 in patients with carcinoma of the cervix," Gynecol. Oncol., 37:276-278, 1990.
McDicken and Rainey, "The immunohistological demonstration of carcinoembryonic antigen in intra-epithelial and invasive squamous carcinoma of the cervix," Histopathol., 7:475-485, 1983.

Moll et al., "Two distinct mechanisms alter p53 in breast cancer: Mutation and nuclear exclusion," Proc. Natl. Acad. Sci. USA, 89:7262-7266, 1992.
Moll et al., "Wild-type p53 protein undergoes cytoplasmic sequestration in undifferentiated neuroblastomas but not in differentiated tumors," Proc. Natl. Acad. Sci. USA, 92:4407-4411, 1995.
Nam et al., "Urinary gonadotropin fragment, a new tumor marker," Gynecol. Oncol., 38:66-70, 1990.
Pectasides et al., "Squamous cell carcinoma antigen, tumor-associated trypsin inhibitor, and carcinoembryonic antigen for monitoring cervical cancer," Am. J. Clin. Oncol., 17(4):307-312, 1994.
Rutanen et al., "Carcinoembryonic antigen in malignant and nonmalignant gynecologic tumors: Circulating levels and tissue localization," Cancer, 42:581-590, 1978.
Silber et al., "DNA polymerase .beta., apurinic/apyrimidinic endonuclease and O.sup.6 -methylguanine-DNA methyltransferase activity in brain tumors and adjacent normal brain," Proc. Am. Assoc. Cancer Res. Ann. Mtg, 36:550, Abstract #3275, 1995.
Stenmark-Askmalm et al., "Cellular accumulation of p53 protein: an independent prognostic factor in stage II breast cancer," Eur. J. Cancer, 30A(2):175-180, 1994.
Takahashi and Suzuki, "DNA synthesis-associated nuclear exclusion of p53 in normal human breast epithelial cells in culture," Oncogene, 9(1):183-188, 1994.
Toki and Yajima, "Immunohistochemical localization of carcinoembryonic antigen (CEA) in squamous cell carcinoma of the uterine cervix: Prognostic significance of localization pattern of CEA," Tohoku J. Exp. Med., 165:25-32, 1991.
van Nagell et al., "Carcinoembryonic antigen in carcinoma of the uterine cervix: Antigen distribution in primary and metastatic tumors," Cancer, 49:379-383, 1982.
Verlooy et al., "Clinical significance of squamous cell carcinoma antigen in cancer of the human uterine cervix," Gynecol. Obstet. Invest., 32:55-58, 1991.
Yao et al., "Apoptosis in human adenocarcinoma HT29 cells induced by exposure to hypoxia," J. Nat'l. Cancer Instit., 87(2):117-122, 1995.
Zerrahn et al., "Correlation between the conformational phenotype of p53 and its subcellular location," Oncogene, 7(7);1371-1381, 1992.

ART-UNIT: 162
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ATTY-AGENT-FIRM: Fulbright & Jaworski

ABSTRACT:

Disclosed are methods and compositions for identifying, monitoring and treating premalignant and malignant conditions in a human subject. The present invention further discloses methods and compositions for determining cells undergoing apoptosis, and for increasing the efficacy of a cancer therapy. The methods involve the use of apurinic/apyrimidinic endonuclease (APE), independently, as a marker for (pre)malignant conditions and for apoptosis. Also described are polyclonal antibody preparations for use in methods for detecting APE and methods for modulating expression susceptibility of cells to apoptosis.

12 Claims, 57 Drawing figures

☐ 3. Document ID: US 6070126 A

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US-PAT-NO: 6070126
DOCUMENT-IDENTIFIER: US 6070126 A

TITLE: Immunobiologically-active linear peptides and method of identification

DATE-ISSUED: May 30, 2000

INVENTOR-INFORMATION:

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ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
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APPL-NO: 9/ 097078
DATE FILED: June 12, 1998

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATION This application claims the benefit of U.S. Provisional Application Ser. No. 60/049,613 filed on Jun. 13, 1997.

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US-CL-ISSUED: 702/19; 530/300
US-CL-CURRENT: 702/19; 530/300
FIELD-OF-SEARCH: 530/300, 702/19

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4554101	November 1985	Hopp	260/112.5
5807978	September 1998	Kokolus et al.	530/300

OTHER PUBLICATIONS

Abramowitz, M., Stegun, I.,(eds) "Handbook of Mathematical Functions", National Bureau of Standards Applied Mathematics Series, #55, 71-79, 1964.
Atherton et al., "Peptide Synthesis", Tetrahedron, 44:843-857, 1988.
Barany et al., Solid-Phase Peptide Synthesis, The Peptides, 2: 1-284, 1988.
Fynan et al., "DNA vaccines: Protective immunization by parenteral, mucosal, and gene-gun inoculations", Proc. Natl. Acad. Sci. USA, 90:11478-11482, Dec. 1993.
Henttu et al., "cDNA Coding for the Entire Human Prostate Specific Antigen Shows High Homologies to the Human Tissue Kallikrein Genes", Biochemical and Biophysical Research Communication, 160: 903-910, 1989.
Hopp et al., "Prediction of protein antigenic determinants from amino acid sequences", Proc. Natl. Acad. Sci. USA, 78(6):3824-3828, Jun. 1981.
Kyte et al., "A Simple Method for Displaying the Hydropathic Character of a Protein", J. Mol. Biol., 157:105-132, 1982.
Pellequer et al., "Predicting Location of Continuous Epitopes in Proteins from Their Primary Structure", Methods in Enzymology, 203:176-201, 1991.
Robinson, HL, "DNA Vaccines", (Abstract) Seminars in Immunology, 9(5) 271, Oct. 1997.
Rosenblum et al., "Amino Acid Sequence Analysis, Gene Construction, Cloning, and Expression of Gelonin, a Toxin Derived from Gelonium multiflorum", J. Interferon and Cytokine Research, 15:547-555, 1995.

ART-UNIT: 163
PRIMARY-EXAMINER: Carlson; Karen Cochrane
ATTY-AGENT-FIRM: Fuierer; Marianne Ellis; Howard M.

ABSTRACT:

The present invention relates to identifying protein epitopes and more particularly to a novel method for identifying, determining the location, optimal length of amino acid residues and immunobiological potency of protein epitopes by applying a custom negative cosine function fit algorithm to a protein hydropathy scale. This fit analysis is supplemented with experimental immunobiological data. The amino acid sequence of the protein epitopes of the present invention exhibit a hydrophobic-hydrophilic-hydrophobic hydropathy pattern of an approximately fixed length in a given protein.

8 Claims, 6 Drawing figures

☐ 4. Document ID: US 6051230 A

L10: Entry 4 of 11 File: USPT Apr 18, 2000

US-PAT-NO: 6051230
DOCUMENT-IDENTIFIER: US 6051230 A

TITLE: Compositions for targeting the vasculature of solid tumors

DATE-ISSUED: April 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Board of Regents, The University of Texas System	Austin	TX			02

APPL-NO: 8/ 457869
DATE FILED: June 1, 1995

PARENT-CASE:
The present application is a division of copending application Ser. No. 08/350,212, filed Dec. 5, 1994, which is continuation-in-part of U.S. patent application Ser. No. 08/205,330, filed Mar. 2, 1994 (U.S. Pat. No. 5,855,866); which is a continuation-in-part of U.S. Pat. application Ser. No. 07/846,349, filed Mar. 05, 1992 (now abandoned). The entire text and figures of which disclosures are specifically incorporated by reference herein without disclaimer.

INT-CL: [7] A61K 39/395, C07K 16/00
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US-CL-CURRENT: 424/178.1; 424/179.1, 424/180.1, 424/181.1, 424/182.1, 424/183.1, 530/387.1, 530/387.7, 530/388.1, 530/388.2
FIELD-OF-SEARCH: 424/183.1, 424/178.1, 424/179.1, 424/180.1, 424/181.1, 424/182.1, 530/387.1, 530/387.7, 530/388.1, 530/388.2

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4456550	June 1984	Dvorak et al.	N/A
4472509	September 1984	Gansow et al.	N/A
4536387	August 1985	Sakamoto et al.	N/A
5021236	June 1991	Gries et al.	N/A
5081034	January 1992	Bevilacqua et al.	N/A
5284931	February 1994	Springer et al.	N/A
5342757	August 1994	Garin-Chesa et al.	N/A
5399346	March 1995	Anderson et al.	N/A
5403713	April 1995	Bevilacqua et al.	N/A
5632991	May 1997	Gimbrone, Jr.	N/A
5659013	August 1997	Senge et al.	N/A
5660827	August 1997	Thorpe et al.	424/152.1
5776427	July 1998	Thorpe et al.	424/1.49
5855866	January 1999	Thorpe et al.	424/1.49
5863538	January 1999	Thorpe et al.	424/136.1

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 81/01145	April 1981	WOX	
WO 90/03801	April 1990	WOX	
WO 90/12585	November 1990	WOX	
WO 90/13300	November 1990	WOX	
WO 92/12729	June 1992	WOX	
WO 92/19646	November 1992	WOX	
WO 93/08210	April 1993	WOX	
WO 93/08473	April 1993	WOX	
WO 93/17715	September 1993	WOX	
WO 94/05328	March 1994	WOX	
WO 94/11202	May 1994	WOX	
WO 94/11499	May 1994	WOX	

OTHER PUBLICATIONS

Osborn et al., "Leukocyte Adhesion to Endothelium in Inflammation," Cell, 62:3-6, 1990.
June et al., "Role of the CD28 Receptor in T-Cell Activation," Immunology Today, 11(6):211-216, 1990.
Denekamp, "Vascular Attack as a Therapeutic Strategy for Cancer," Cancer and Metastasis Reviews, 9:267-282, 1990.
Scott et al., "Anti-CD3 Antibody Induces Rapid Expression of Cytokine Genes In Vivo," The Journal of Immunology, 145(7):2183-2188, 1990.
O'Connell & Edidin, "A Mouse Lymphoid Endothelial Cell Line Immortalized by Simian Virus 40 Binds Lymphocytes and Retains Functional Characteristics of Normal Endothelial Cells," The Journal of Immunology, 144(2):521-525, 1990.
Ledbetter et al., "CD 28 Ligation in T-Cell Activation: Evidence for Two Signal Transduction," Abstract only, Blood, 75(7):1531-1539, 1990.
Watanabe et al., "Exogenous Expression of Mouse Interferon .gamma. cDNA in Mouse Neuroblastoma C1300 Cells Results in Reduced Tumorigenicity by Augmented Anti-Tumor Immunity," Proceedings of the National Academy of Scientists, 86:9546-9460, 1989.
Schutt et al., "Human Monocyte Activation Induced by an Anti-CD14 Monoclonal

Antibody," Immunology Letters, 19:321-328, 1988.
Thorpe et al., "Improved Antitumor Effects of Immunotoxins Prepared with Deglycosylated Ricin A-Chain and Hindered Disulfide Linkages," Cancer Research, 48:6396-6403, 1988.
Glennie et al., "Preparation and Performance of Bispecific (F(ab'.gamma.).sub.2 Antibody Containing Thioether-Linked Fab'.gamma. Fragments," The Journal of Immunology, 139(7):2367-2375, 1987.
Bevilacqua et al., "Identification of an Inducible Endothelial-Leukocyte Adhesion Molecule," Proceedings of the National Academy of Scientists, 84:9238-9242, 1987.
Cotran et al., "Induction and Detection of a Human Endothelial Activation Antigen In Vivo," Abstract only, The Journal of Experimental Medicine, 164(2):661-666, 1986.
Groenewegen et al., "Lymphokine Dependence of In Vivo Expression of MHC Class II Antigens by Endothelium," Nature, 316:361-263, 1985.
Moretta et al., Abstract only, The Journal of Experimental Medicine, 162(3):823-838, 1985.
Vaickus & Foon, "Overview of Monoclonal Antibodies in the Diagnosis and Therapy of Cancer," Cancer Investigation, 93(2):295-209, 1991.
Hagemeier et al., "A Monoclonal Antibody Reacting with Endothelial Cells of Budding Vessels in Tumors and Inflammatory Tissues, and Non-Reactive with Normal Adult Tissues," International Journal of Cancer, 38:481-488, 1986.
Duijvestijn et al., "Lymphoid Tissue- and Inflammation-Specific Endothelial Cell Differentiation defined by Monoclonal Antibodies," The Journal of Immunology, 138(3):713-719, 1987.
Murray et al., "Vascular Markers for Murine Tumours," Radiotherapy and Oncology, 16:221-234, 1989.
Schlingemann et al., "Monoclonal Antibody PAL-E Specific for Endothelium," Laboratory Investigation, 52(1):71-76, 1985.
Bruland et al., "New Monoclonal Antibodies Specific for Human Sarcomas," International Journal of Cancer, 38:27-31, 1986.
Reisfeld et al., "Human Tumor-Associated Antigens Defined by Monoclonal Antibodies," CRC Critical Reviews in Immunology, 5(1):27-53, 1984.
Schlom et al., "Monoclonal Antibodies Reactive with Breast Tumor-Associated Antigens," Advances in Cancer Research, 43:143-173, 1985.
Kaplan, "The Diagnostic and Therapeutic Use of Monoclonal Antibodies in Colorectal Cancer," Hematology/Oncology Clinics of North American, 3(1):125-134, 1989.
Smith & Teng, "Clinical Applications of Monoclonal Antibodies in Gynecologic Oncology," Cancer, 60:2068-2074, 1987.
Stavrou, "Monoclonal Antibodies in Neuro-Oncology," Neurosurgery Review, 13:7-18, 1990.
Shepard et al., "Monoclonal Antibody Therapy of Human Cancer: Taking the HEr2 Protooncogene to the Clinic," Journal of Clinical Immunology, 11(3):117-127, 1991.
Szymendera, "Clinical Usefulness of Three Monoclonal Antibody-Defined Tumor Markers: CA 19-9, CA 50, and CA 125," Tumour Biology, 7:333-342, 1986.
Catane & Longo, "Monoclonal Antibodies for Cancer Therapy," Israel Journal of Medical Sciences, 24:471-476, 1988.
Greiner et al., "Applications of Monoclonal Antibodies and Recombinant Cytokines for the Treatment of Human Colorectal and Other Carcinomas," Journal of Surgical Oncology Supplement, 2:9-13, 1991.
Thor & Edgerton, "Monoclonal Antibodies Reactive with Human Breast or Ovarian Carcinoma: In Vivo Applications," Seminars in Nuclear Medicine, 19(4):295-308, 1989.
Thorpe et al., "Selective Killing of Proliferating Vascular Endothelial Cells by an Anti-Fibronectin Receptor Immunotoxin," 16th LH Gray Conference, University of Manchester Institute of Science and Technology, Sep. 17-21, 1990.
Thorpe et al., "Targeting to Proliferating Vascular Endothelium," International Symposium on Angiogenesis, St. Gallen, Switzerland, Abstract, Mar. 13-15, 1991.
Ghose, Tarun I. et al., "Preparation of Antibody-Linked Cytotoxic Agents," Methods in Enzymology, 93:280-333, 1983.
Knowles, Phillip P. and Thorpe, Philip E., "Purification of Immunotoxins Containing Ricin A-Chain and Abrin A-Chain Using Blue Sepharose CL-6B," Analytical Biochemistry, 160:440-443, 1987.

Wang, Theodore S.T. et al., "Photoreactive In-Cyclodextrin Inclusion Complex: a New Heterobifunctional Reagent for Antibody Labeling," Nuclear Medicine and Biology, 19(8):897-902, 1992.
PCT Search Report mailed Jun. 25, 1993.
Alvarez, J.A. et al., "Localization of Basic Fibroblast Growth Factor and Vascular Endothelial Growth Factor in Human Glial Neoplasms," Modern Pathology, 5(3):303-307, 1992.
Brown, Lawrence F. et al., "Expression of Vascular Permeability Factor (Vascular Endothelial Growth Factor) and Its Receptors in Adenocarcinomas of the Gastrointestinal Tract," Cancer Research, 53:4727-4735, 1993.
Kim, K. Jin et al., "Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumor growth in vivo," Nature, 362:841-844, 1993.
Dvorak, Harold F. et al., "Distribution of Vascular Permeability Factor (Vascular Endothelial Growth Factor) in Tumors: Concentration in Tumor Blood Vessels," J. Exp. Med., 174:1275-1278, 1991.
Gerlach, Herwig et al., "Enhanced Responsiveness of Endothelium in the Growing/Motile State to Tumor Necrosis Factor/Cachectin," J. Exp. Med., 170:913-931, 1989.
Gougos, Anne et al., "Identification of distinct epitopes of endoglin, an RGD-containing glycoprotein of endothelial cells, leukemic cells, and syncytiotrophoblasts," International Immunology, 4(1):83-92, 1991.
Gougos, Anne et al., "Identification of a Human Endothelial Cell Antigen with Monoclonal Antibody 44G4 Produced Against a Pre-B Leukemic Cell Line," The Journal of Immunology, 141:1925-1933, 1988.
Gougos, Anne et al., "Biochemical Characterization of the 44G4 Antigen from the Hoon Pre-B Leukemic Cell Line," The Journal of Immunology, 141:1934-1940, 1988.
Hagemeier, Hans-Hermann et al., "A Monoclonal Antibody Reacting with Endothelial Cells of Budding Vessels in Tumors and Inflammatory Tissues, and Non-Reactive with Normal Adult Tissues," Int. J. Cancer, 38:481-488, 1986.
Jakeman, Lyn B. et al., "Binding Sites for Vascular Endothelial Growth Factor Are Localized on Endothelial Cells in Adult Rat Tissues," J. Clin. Invest., 89:244-253, 1992.
Nabel, Elizabeth G. et al., "Recombinant fibroblast growth factor-1 promotes intimal hyperplasia and angiogenesis in arteries in vivo," Nature, 362:844, 1993.
O'Connell, P.J. et al., "Endoglin: a 180-kD endothelial cell and macrophage restricted differentiation molecule," Clin. Exp. Immunol., 90:154-159, 1992.
Plate, K.H. et al., "Up-Regulation of Vascular Endothelial Growth Factor and Its Cognate Receptors in a Rat Glioma Model of Tumor Angiogenesis," Cancer Research, 53(23):5822-5827, 1993.
Plate, Karl H. et al., "Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo," Nature, 359:845-848, 1992.
Rettig, Wolfgang J. et al., "Identification of endosialin, a cell surface glycoprotein of vascular endothelial cells in human cancer," Proc. Natl. Acad. Sci. USA, 89:10832-10836, 1992.
Sarma, Vidya et al., "Cloning of a Novel Tumor Necrosis Factor-.alpha.-Inducible Primary Response Gene that is Differentially Expressed in Development and Capillary Tube-Like Formation in vitro," The Journal of Immunology, 148:3302-3312, 1992.
Senger, Donald R. et al., "The Vascular permeability factor (VPF,VEGF) in tumor biology," Cancer and Metatasts Reviews, 12:303-324, 1993.
Shweiki, Dorit et al., "Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis," Nature, 359:843-845, 1992.
Wang, J.M. et al., "Monoclonal Antibody Detects Heterogeneity in Vascular Endothelium of Tumours and Normal Tissues," Int. J. Cancer, 54:363-370, 1993.
Westphal, Johan R. et al., "A New 180-kDa Dermal Endothelial Cell Activation Antigen: In Vitro and In Situ Characteristics," The Journal of Investigative Dermatology, 100(1):27-34, 1993.
Yeo, Kiang-Teck et al., "Vascular Permeability Factor (Vascular Endothelial Growth Factor) in Guinea Pig and Human Tumor and Inflammatory Effusions," Cancer Research, 53:2912-2918, 1993.
Buring et al., "Endoglin is expressed on a subpopulation of immature erythroid cells of normal human bone marrow," Leukemia, 5(10):841-847, 1991.
Dvorak et al., "Structure of Solid Tumors and Their Vasculature: Implications for Therapy with Monoclonal Antibodies," Cancer Cells, 3(3):77-85, 1991.

Gougos & Letarte, "Primary Structure of Endoglin, an RGD-containing Glycoprotein of Human Endothelial Cells," The Journal of Biological Chemistry, 265(15):8361-8364, 1990.
UTSD:344; U.S. application No. 08/295,868, Nationalization of PCT/US/01956; U.S. Filing date Sep. 6, 1994.
UTSD:393; U.S. application No. 08/205,330; filed Mar. 2, 1994.
UTSD:430; U.S. application No. 08/350,212; filed Dec. 5, 1994.
UTSD:451; U.S. application No. 08/456,495, filed Jun. 1, 1995; Divisional of UTSD:430.
UTSD:452; U.S. application No. 08/457,487, filed Jun. 1, 1995; Divisional of UTSD:430.
UTSD:453; U.S. application No. 08/457,229, filed Jun. 1, 1995; Divisional of UTSD:430.
UTSD:454; U.S. application No. 08/457,031, filed Jun. 1, 1995; Divisional of UTSD:430.
Osband and Ross, "Problems in the Investigational Study and Clinical Use of Cancer Immunotherapy," Immunotherapy, 11:193-195, 1990.
Chatterjee, et al., Idiotypic antibody immunotherapy of cancer, Cancer Immunol. Immunotherapy, 38:75-82, 1994.
Allowed Claims of U.S. application No. 08/327,709, Dvorak.
Songsivilai & Lachmann, "Bispecific antibody: a tool for diagnosis and treatment of disease", Clin. exp. Immunol., 79, 315-3321 (1990).
Dermer, "Another Anniversary for the War on Cancer", Bio/technology, 12, 320 (1994).
Pober and Cotran, "What Can Be Learned From the Expression of Endothelial Adhesion Molecules in Tissues?", Laboratory Investigation, 64(3), 301-305 (1991).
Aoyagi, "Distribution of Plasma Fibronectin in the Metastatic Lesion of Cancer: Experimental Study by Autoradiography," Thrombosis Research, 49:265-75, 1988.
Balza et al., "Production and Characterization of Monoclonal Antibodies Specific for Different Epitopes of Human Tenascin," FEBS 332(1,2):39-43, 1993.
Bjorndahl, et al., "Human T Cell Activation: Differential Response to Anti-CD28 As Compared to Anti-CD3 Monoclonal Antibodies," Eur. J. Immunol., 19:881-87, 1989.
Blanchard, et al., "Infiltration of Interleukin-2-Inducible Killer Cells in Ascitic Fluid and Pleural Effusions of Advanced Cancer Patients," Cancer Research, 48:6321-27, 1988.
Bohlen, et al., "Cytolysis of Leukemic B-Cells by T-Cells Activated via Two Bispecific Antibodies," Cancer Research, 53:4310-14, 1993.
Borsi, et al., "Expression of Different Tenascin Isoforms in Normal, Hyperplastic and Neoplastic Human Breast Tissues," Int. J. Cancer, 52:688-92, 1992.
Boyer, et al., "Differential Induction by Interferons of Major Histocompatibility Complex-Encoded and Non-Major Histocompatibility Complex-Encoded Antigens in Human Breast and Ovarian Carcinoma Cell Lines," Cancer Research, 49:2928-34, 1989.
Burton-Wurster, et al., "Expression of the Ed B Fibronectin Isoform in Adult Human Articular Cartilage," Biochemical and Biophysical Research Communication 165(2):782-87, 1989.
Collins, et al., "Immune Interferon Activates Multiple Class II Major Histocompatibility Complex Genes and the Associated Invariant Chain Gene in Human Endothelial Cells and Dermal Fibroblasts," Proc. Natl. Acad. Sci. USA, 81:4917-21, 1984.
Carnemolla et al., "A Tumor-associated Fibronectin Isoform Generated by Alternative Splicing of Messenger RNA Precursors," The Journal of Cell Biology, 108:1139-48, 1989.
Carnemolla et al., "The Inclusion of the Type III Repeat ED-B in the Fibronectin Molecule Generates Conformational Modifications that Unmask a Cryptic Sequence," The Journal of Biological Chemistry, 267(34):24589:92, 1992.
Carnemolla, et al., "Phage Antibodies with Pan-Species Recognition of the Oncofoetal Angiogenesis Marker Fibronectin ED-B Domain," Int. J. Cancer 68:397-405, 1996.
Castellani, et al., "The Fibronectin Isoform Containing the ED-B Oncofoetal Domain: A Marker of Angiogenesis," Int. J. Cancer, 59:612-18, 1994.
Conforti, et al., "Human Endothelial Cells Express Integrin Receptors on the

Luminal Aspect of Their Membrane," Blood 80(2):437-46, 1992.
Dillman, "Monoclonal Antibodies for Treating Cancer," Annals of Internal Medicine, 111(7) 592-600, 1989.
Farnoud, et al., "Fibronectin Isoforms Are Differentially Expressed in Normal and Adenomatous Human Anterior Pituitaries," Int. J. Cancer, 61:27-34, 1995.
Garin-Chesa, et al., "Cell Surface Glycoprotein of Reactive Fibroblasts As A Potential Antibody Target in Human Epithelial Cancers," Proc. Natl. Acad. Sci. USA, 87:7235-39, 1990.
Groenewegen, et al., "Lymphokine Dependence of In Vivo Expression of MHC Class II Antigens by Endothelium," Nature, 316:361-63, 1985.
Harris and Emery, "Therapeutic Antibodies--The Coming of Age," Btech, 11:42-44, 1993.
June, et al., "T-Cell Proliferation Involving the CD28 Pathway Is Associated with Cyclosporine-Resistant Interleukin 2 Gene Expression," Molecular and Cellular Biology 7(12):4473-81, 1987.
Kaczmarek, et al., "Distribution of Oncofetal Fibronectin Isoforms in Normal Hyperplastic and Neoplastic Human Breast Tissues," Int. J. Cancer, 58:11-16, 1994.
Koulova et al., "The CD28 Ligand B7/BB1 Provides Costimulatory Signal for Alloactivation of CD4.sup.+ T Cells," J. Exp. Med. 173:759-62, 1991.
Kurosawa, et al., "Early Appearance and Activation of Natural Killer Cells in Tumor-Infiltrating Lymphoid Cells During Tumor Development," Eur. J. Immunol. 23:1029-33, 1993.
Lampugnani, et al., "The Role of Integrins in the Maintenance of Endothelial Monolayer Integrity," The Journal of Cell Biology, 112(3):479-90, 1991.
Linnala, et al., "Human Amnion Epithelial Cells Assemble Tenascins and Three Fibronectin Isoforms in the Extracellular Matrix," FEBS, 314(1,2):74-78, 1993.
Maeda, et al., "Production and Characterization of Tumor Infiltrating Lymphocyte Clones Derived from B16-F10 Murine Melanoma," The Journal of Investigative Dermatology 97(2):183-89, 1991.
Natali, et al., "Comparative Analysis of the Expression of the Extracellular Matrix Protein Tenascin in Normal Human Fetal, Adult and Tumor Tissues," Int. J. Cancer, 47:811-16, 1991.
Oyama, et al., "Coordinate Oncodevelopmental Modulation of Alternative Splicing of Fibronectin Pre-Messenger RNA at ED-A, ED-B and CS1 Regions in Human Liver Tumors," Cancer Research 53:2005-11, 1993.
Peters, et al., "Expression of the Alternatively Spliced EIIIB Segment of Fibronectin," Cell Adhesion and Communication, 3:67-89, 1995.
Pober et al., "Ia Expression by Vascular Endothelium Is Indcuible by Activated T Cells and by Human .gamma. Interferon," J. Exp. Med. 157:1339-53, 1983.
Pohl, et al., "CD30-Antigen-Specific Targeting and Activation of T Cells via Murine Bispecific Monoclonal Antiodies Against CD3 and CD28: Potential Use for the Treatment of Hodgkin's Lymphoma," Int. J. Cancer, 54:820-27, 1993.
Renner, et al., "Cure of Xenografted Human Tumors by Bispecific Monoclonal Antibodies and Human T Cells," Science, 264:833-35, 1994.
Rettig, et al., "Cell-Surface Glycoproteins of Human Sarcomas: Differential Expression in Normal and Malignant Tissues and Cultured Cells," Proc. Natl. Acad. Sci. USA, 85:3110-14, 1988.
Rettig, et al., Identification of Endosialin, A Cell Surface Glycoprotein of Vascular Endothelial Cells in Human Cancer, Proc. Natl. Acad. Sci. USA, 89:10832-36, 1992.
Rosenberg, Steven, "Lymphokine-Activated Killer Cells: A New Approach to Immunotherapy of Cancer," JNCI 75(4):595-603, 1985.
Rosenberg, et al., "Observations of the Systemic Administration of Autologous Lymphokine-Activated Killer Cells and Recombinant Interleukin-2 to Patients with Metastatic Cancer," The New England Journal of Medicine, 313(23):1485-92, 1985.
Ruiter, et al., "Monoclonal Antibody-Defined Human Endothelial Antigens as Vascular Markers," J. Investigative Dermatol., 93(2):25S-32S, 1989.
Saiki et al., "Anti-metastatic and Anti-invasive Effects of Polymeric Arg-Gly-Asp (RGD) Peptide, Poly(RGD), and Its Analogues," Jpn. J. Cancer Res. 81:660-67, 1990.
Saiki et al., "Inhibition of Tumor Angiogenesis by a Synthetic Cell-Adhesive Polypeptide Containing the Arg-Gly-Asp (RGD) Sequence of Fibronectin, Poly(RGD)," Jpn. J. Cancer Res. 81:668-75, 1990.
Schlingemann, et al., "Differential Expression of Markers for Endothelial Cells,

Pericytes, and Basal Lamina in the Microvasculature of Tumors and Granulation Tissue," Am. J. Pathol., 138(6):1335-47, 1991.
Schwarzbauer, "Alternative Splicing of Fibronectin: Three Variants, Three Functions," BioEssays 13(10)527-33, 1991.
Siri, et al., "Human Tenascin: Primary Structure, Pre-mRNA Splicing Patterns and Localization of the Epitopes Recognized by Two Monoclonal Antibodies," Nucleic Acids Research, 19(3):525-31, 1991.
Steiniger, et al., "Interferon-.gamma. in Vivo. Induction and Loss of Class II MHC Antigens and Immture Myelomonocytic Cells in Rat Organs," Eur. J. Immunol. 18:661-69, 1988.
Street, et al., "In Vivo Administration of Fab'Fragments of Anti-L3T4 (GK1.5) Antibody Inhibits the T Helper Cell Function of Murine Lymph Node Cells," Cellular Immunology 120:75-81, 1989.
Thompson, et al., "CD28 Activation Pathway Regulates the Production of Multiple-T-Cell-Derived Lymphokines/Cytokines," Proc. Natl. Acad. Sci. USA, 86:1333-37, 1989.
Ueda, et al., "Selective Distribution of Fibronectin to a Tumor-Cell Line," Cancer Letters 31:261-65, 1986.
Vartio, et al., "Differential Expression of the ED Sequence-Containing Form of Cellular Fibronectin in Embryonic and Adult Human Tissues," Journal of Cell Science, 88:419-30, 1987.
Welt, et al., "Phase I Localization Study of .sup.131 I-monoclonal Antibody F19 Detecting an Activation Antigen of Neoplastic Stroma," Proceedings of the American Association for Cancer Research, 33:319, 1992, Abstract No. 1900.
Werb, et al., "Signal Transduction through the Fibronectin Receptor Induces Collagenase and Stromelysin Gene Expression," The Journal of Cell Biology., 109:877-89, 1989.
Burgess et al. , "Possible Dissociation of the Heparin-Binding and Mitogenic Activities of Heparin-Binding (Acidic Fibroblast) Growth Factor-1 from Its Receptor-Biding Activities by Site-Directed Mutagenesis of a Single Lysine Residue," J. Cell Biol., 111:2129-2138, 1990.
Gillies and Wesolowski, "Antigen Binding and Biological Activities of Engineered Mutant Chimeric Antibodies and Human Tumor Specificities," Hum. Antibod. Hybridomas, 1(1):47-54, 1990.
Lapierre et al. , "Three Distinct Classes of Regulatory Cytokines Control Endothelial Cell MHC Antigen Expression," J. Exp. Med., 167:794-804, 1988.
Lazar et al. , "Transforming Growth Factor .alpha.: Mutation of Aspartic Acid 47 and Leucine 48 Results in Different Biological Activities," Mol. Cell Biol., 8(3):1247-1252, 1988.
Qian et al. , "Human Peripheral Blood Lymphocytes Targeted with Bispecific Antibodies Release Cytokines That Are Essential for Inhibiting Tumor Growth," J. Immunol., 146(9):3250-3256, 1991.
Tao and Morrison, "Studies of Aglycosylated Chimeric Mouse-Human IgG--Role of Carbohydrate in the Structure and Effector Functions Mediated by the Human IgG Constant Region," J. Immunol., 143(8):2595-2601, 1989.
Waldman, Thomas A., "Monoclonal Antibodies in Diagnosis and Therapy," Science, 252:1657-1662, 1991.
Wen et al. , "Effects of .gamma.-Inteferon on Major Histocompatibility Complex Antigen Expression and Lymphocytic Infiltration in the 9L Gliosarcoma Brain Tumor Model: Implications for Strategies of Immunotherapy," J. Neuroimmunol., 36:57-68, 1992.
Burrows et al., "A Murine Model for Antibody-Directed Targeting of Vascular Endothelial Cells in Solid Tumors," Cancer Research, 52:5954-5962, Nov. 1992.
Burrows and Thorpe, "Targeting the Vasculature of Solid Tumors," Journal of Controlled Release, 28:195-202, Jan. 1994.
Clauss et al., "A Polypeptide Factor Produced by Fibrosarcoma Cells That Induces Endothelial Tissue Factor and Enhances the Procoagulant Response to Tumor Necrosis Factor/Cachetin," The Journal of Biological Chemistry, 265(12):7078-7083, Apr. 1990.
Thorpe and Burrows, "Antibody-Directed Targeting of the Vasculature of Solid Tumors," Breast Cancer Research and Treatment, 36(2):237-251, 1995.
Yamazaki et al., "Bispecific Monoclonal Antibodies with Specificities for Activated Platelets and Thrombolytic Agents, Their Production and Use," Abstract for Canadian Patent Application CA 2039259; Chem Abstracts, 117(11), Abstract #109988.

International Search Report, Mailed Nov. 24, 1995.
Benjamin et al BBRC vol. 171(1) 348-53 (1990).
Li et al Lancet 1994 vol. 344(8915) 82-86.

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ABSTRACT:

The present invention relates generally to methods and compositions for targeting the vasculature of solid tumors using immunological- and growth factor-based reagents. In particular aspects, antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature of solid tumor masses through recognition of tumor vasculature-associated antigens, such as, for example, through endoglin binding, or through the specific induction of endothelial cell surface antigens on vascular endothelial cells in solid tumors.

61 Claims, 37 Drawing figures

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U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4456550	June 1984	Dvorak et al.	260/112R
4472509	September 1984	Gansow et al.	N/A
4536387	August 1985	Sakamoto et al.	424/14
5021236	June 1991	Gries et al.	N/A
5036003	July 1991	Olander et al.	435/20.1
5081034	January 1992	Bevilacqua et al.	N/A
5342757	August 1994	Garin-Chesa et al.	435/7.21
5360896	November 1994	Senoo et al.	530/399
5399346	March 1995	Anderson et al.	424/93.21
5403713	April 1995	Bevilacqua et al.	435/7.1
5571714	November 1996	Dasch et al.	435/240.27
5612212	March 1997	Gewirtz	435/172.3
5632991	June 1997	Gimbrone, Jr.	424/178.1
5659013	August 1997	Senger et al.	530/350

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 81/01145	April 1981	WOX	
WO 90/03801	April 1990	WOX	
WO 90/13300	November 1990	WOX	
WO 90/12585	November 1990	WOX	
WO 92/12729	August 1992	WOX	
WO 92/19646	November 1992	WOX	
WO 93/08210	April 1993	WOX	
WO 93/08473	April 1993	WOX	
WO 93/17715	September 1993	WOX	
WO 94/05328	March 1994	WOX	
WO 94/10202	May 1994	WOX	
WO 94/11499	May 1994	WOX	

OTHER PUBLICATIONS

Osband and Ross, "Problems in the Investigational Study and Clinical Use of Cancer Immunotherapy," Immunotherapy, 11:193-195, 1990.
Chatterjee, et al., Idiotypic antibody immunotherapy of cancer Cancer Immunol. Immunotherapy, 38:75-82, 1994.
Plate, Karl H. et al., "Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo," Nature, 359:845-848, 1992.
Rettig, Wolfgang J. et al., "Identification of endosialin, a cell surface glycoprotein of vascular endothelial cells in human cancer," Proc. Natl. Acad. Sci. USA, 89:10832-10836, 1992.
Sarma, Vidya et al., "Cloning of a Novel Tumor Necrosis Factor-.alpha.-Inducible Primary Response Gene that is Differentially Expressed in Development and

Capillary Tube-Like Formation in vitro," The Journal of Immunology, 148:3302-3312, 1992.
Senger, Donald R. et al., "Vascular permeability factor (VPF, VEGF) in tumor biology," Cancer and Metatasts Reviews, 12:303-324, 1993.
Shweiki, Dorit et al., "Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis," Nature, 359:843-845, 1992.
Wang, J.M. et al., "A Monoclonal Antibody Detects Heterogeneity in Vascular Endothelium of Tumours and Normal Tissues," Int. J. Cancer, 54:363-370, 1993.
Westphal, Johan R. et al., "A New 180-kDa Dermal Endothelial Cell Activation Antigen: In Vitro and In Situ Characteristics," The Journal of Investigative Dermatology,100(1):27-34, 1993.
Yeo, Kiang-Teck et al., "Vascular Permeability Factor (Vascular Endothelial Growth Factor) in Guinea Pig and Human Tumor and Inflammatory Effusions," Cancer Research, 53:2912-2918, 1993.
Aoyagi, "Distribution of Plasma Fibronectin in the Metastatic Lesion of Cancer: Experimental Study by Autoradiography," Thrombosis Research, 49:265-75, 1988.
Balza et al., "Production and Characterization of Monoclonal Antibodies Specific for Different Epitopes of Human Tenascin," FEBS 332(1,2):39-43, 1993.
Bjorndahl, et al., "Human T Cell Activation: Differential Response to Anti-CD28 As Compared to Anti-CD3 Monoclonal Antibodies," Eur. J. Immunol. 19:881-87, 1989.
Blanchard, et al., "Infiltration of Interleukin-2-Inducible Killer Cells in Ascitic Fluid and Pleural Effusions of Advanced Cancer Patients," Cancer Research, 48:6321-27, 1988.
Bohlen, et al., "Cytolysis of Leukemic B-Cells by T-Cells Activated via Two Bispecific Antibodies," Cancer Research, 53:4310-14, 1993.
Borsi, et al., "Expression of Different Tenascin Isoforms in Normal, Hyperplastic and Neoplastic Human Breast Tissues," Int. J. Cancer, 52:688-92, 1992.
Boyer, et al., "Differential Induction by Interferons of Major Histocompatibility Complex-Encoded and Non-Major Histocompatibility Complex-Encoded Antigens in Human Breast and Ovarian Carcinoma Cell Lines," Cancer Research, 49:2928-34, 1989.
Burton-Wurster, et al., "Expression of the Ed B Fibronectin Isoform in Adult Human Articular Cartilage," Biochemical and Biophysical Research Communication 165(2):782-87, 1989.
Collins, et al., "Immune Interferon Activates Multiple Class II Major Histocompatibility Complex Genes and the Associated Invariant Chain Gene in Human Endothelial Cells and Dermal Fibroblasts," Proc. Natl. Acad. Sci. USA, 81:4917-21, 1984.
Carnemolla et al., "A Tumor-associated Fibronectin Isoform Generated by Alternative Splicing of Messenger RNA Precursors," The Journal of Cell Biology, 108:1139-48, 1989.
Carnemolla et al., "The Inclusion of the Type III Repeat ED-B in the Fibronectin Molecule Generates Conformational Modifications that Unmask a Cryptic Sequence," The Journal of Biological Chemistry, 267(34):24589-92, 1992.
Carnemolla, et al., "Phage Antibodies with Pan-Species Recognition of the Oncofoetal Angiogenesis Marker Fibronectin ED-B Domain," Int. J. Cancer, 68:397-405, 1996.
Castellani, et al., "The Fibronectin Isoform Containing the ED-B Oncofoetal Domain: A Marker of Angiogenesis," Int. J. Cancer, 59:612-18, 1994.
Conforti, et al., "Human Endothelial Cells Express Integrin Receptors on the Luminal Aspect of Their Membrane," Blood 80(2):437-46, 1992.
Dillman, "Monoclonal Antibodies for Treating Cancer," Annals of Internal Medicine, 111(7): 592-600, 1989.
Farnoud, et al., "Fibronectin Isoforms Are Differentially Expressed in Normal and Adenomatous Human Anterior Pituitaries," Int. J. Cancer, 61:27-34, 1995.
Garin-Chesa, et al., "Cell Surface Glycoprotein of Reactive Stromal Fibroblasts As A Potential Antibody Target in Human Epithelial Cancers," Proc. Natl. Acad. Sci. USA, 87:7235-39, 1990.
Groenewegen, et al., "Lymphokine Dependence of In Vivo Expression of MHC Class II Antigens by Endothelium," Nature, 316:361-63, 1985.
Harris and Emery, "Therapeutic Antibodies -The Coming of the Age," Btech, 11:42-44, 1993.
June, et al., "T-Cell Proliferation Involving the CD28 Pathway Is Associated

with Cyclosporine-Resistant Interleukin 2 Gene Expression," Molecular and Cellular Biology 7(12):4473-81, 1987.
Kaczmarek, et al., "Distribution of Oncofetal Fibronectin Isoforms in Normal Hyperplastic and Neoplastic Human Breast Tissues," Int. J. Cancer, 58:11-16, 1994.
Koulova et al., "The CD28 Ligand B7/BB1 Provides Costimulatory Signal for Alloactivation of CD4.sup.+ T Cells," J. Exp. Med. 173:759-62, 1991.
Kurosawa, et al., "Early Appearance and Activation of Natural Killer Cells in Tumor-Infiltrating Lymphoid Cells During Tumor Development," Eur. J. Immunol. 23:1029-33, 1993.
Lampugnani, et al., "The Role of Integrins in the Maintenance of Endothelial Monolayer Integrity," The Journal of Cell Biology, 112(3):479-90, 1991.
Linnala, et al., "Human Amnion Epithelial Cells Assemble Tenascins and Three Fibronectin Isoforms in the Extracellular Matrix," FEBS, 314(1,2):74-78, 1993.
Maeda, et al., "Production and Characterization of Tumor Infiltrating Lymphocyte Clones Derived from B16-F10 Murine Melanoma," The Journal of Investigative Dermatology 97(2):183-89, 1991.
Natali, et al., "Comparative Analysis of the Expression of the Extracellular Matrix Protein Tenascin in Normal Human Fetal, Adult and Tumor Tissues," Int. J. Cancer, 47:811-16, 1991.
Oyama, et al., "Coordinate Oncodevelopmental Modulation of Alternative Splicing of Fibronectin Pre-Messenger RNA at ED-A, ED-B and CS1 Regions in Human Liver Tumors," Cancer Research 53:2005-11, 1993.
Peters, et al., "Expression of the Alternatively Spliced EIIIB Segment of Fibronectin," Cell Adhesion and Communication, 3:67-89, 1995.
Pober et al., "Ia Expression by Vascular Endothelial Is Indcuible by Activated T Cells and by Human .gamma. Interferon," J. Exp. Med. 157: 1339-53, 1983.
Pohl, et al., "CD30-Antigen-Specific Targeting and Activation of T Cells via Murine Bispecific Monoclonal Antibodies Against CD3 and CD28: Potential Use for the Treatment of Hodgkin's Lymphoma," Int. J. Cancer, 54:820-27, 1993.
Renner, et al., "Cure of Xenografted Human Tumors by Bispecific Monoclonal Antibodies and Human T Cells," Science, 264:833-35, 1994.
Rettig, et al., "Cell-Surface Glycoproteins of Human Sarcomas: Differential Expression in Normal and Malignant Tissues and Cultured Cells," Proc. Natl. Acad. Sci. USA, 85:3110-14, 1998.
Rettig, et al., Identification of Endosialin, A Cell Surface Glycoprotein of Vascular Endothelial Cells in Human Cancer, Proc. Natl. Acad. Sci. USA, 89:10832-36, 1992./
Rosenberg, Steven, "Lymphokine-Activated Killer Cells: A New Approach to Immunotherapy of Cancer," JNCI 75(4):595-603, 1985.
Rosenberg, et al., "Observations of the Systemic Administration of Autologous Lymphokine-Activated Killer Cells and Recombinant Interleukin-2 to Patients with Metastatic Cancer," The New England Journal of Medicine, 313(23):1485-92, 1985.
Ruiter, et al., "Monoclonal Antibody-Defined Human Endothelial Antigens as Vascular Markers," J. Investigative Dermatol., 93(2):25S-32S, 1989.
Saiki et al., "Anti-metastatic and Anti-invasive Effects of Polymeric Arg-Gly-Asp (RGD) Peptide, Poly(RGD), and Its Analogues," Jpn. J. Cancer Res. 81:660-67, 1900.
Saiki, et al., "Inhibition of Tumor Angiogenesis by a Synthetic Cell-Adhesive Polypeptide Containing the Arg-Gly-Asp (RGD) Sequence of Fibronectin, Poly(RGD)," Jpn. J. Cancer Res. 81:668-75, 1990.
Schlingemann, et al., "Differential Expression of Markers for Endothelial Cells, Pericytes, and Basal Lamina in the Microvasculature of Tumors and Granulation Tissue," Am. J. Pathol., 138(6):1335-47, 1991.
Schwarzbauer, "Alternative Splicing of Fibronectin: Three Variants, Three Functions," BioEssays 13(10)527-33, 1991.
Siri, et al., "Human Tenascin: Primary Structure, Pre-mRNA Splicing Patterns and Localization of the Epitopes Recognized by Two Monoclonal Antibodies," Nucleic Acids Research, 19(3):525-31, 1991.
Steiniger, et al., "Interferon-.gamma. in Vivo. Induction and Loss of Class II MHC Antigens and Immture Myelomonocytic Cells in Rat Organs," Eur. J. Immunol. 18:661-69, 1988.
Street, et al., "In Vivo Administration of Fab'Fragments of Anti-L3T4 (GK1.5) Antibody Inhibits the T Helper Cell Function of Murine Lymph Node Cells," Cellular Immunology 120:75-81, 1989.

Thompson, et al., "CD28 Activation Pathway Regulates the Production of Multiple T-Cell-Derived Lymphokines/Cytokines," Proc. Natl. Acad. Sci. USA, 86:1333-37, 1989.
Ueda, et al., "Selective Distribution of Fibronectin to a Tumor-Cell Line," Cancer Letters 31:261-65, 1986.
Vartio, et al., "Differential Expression of the ED Sequence-Containing Form of Cellular Fibronectin in Embryonic and Adult Human Tissues," Journal of Cell Science, 88:419-30, 1987.
Welt, et al., "Phase I Localization Study of.sup.131 I-monoclonal Antibody F19 Detecting an Activation Antigen of Neoplastic Stroma," Proceedings of the American Association for Cancer Research, 33:319, 1992, Abstract No. 1900.
Werb, et al., "Signal Transduction through the Fibronectin Receptor Induces Collagenase and Stromelysin Gene Expression," The Journal of Cell Biology, 109:877-89, 1989.
Songsivilai & Lachmann, "Bispecific antibody: a tool for diagnosis and treatment of disease", Clin. exp. Immunol., 79,315-321 (1990).
Dermer, "Another Anniversary for the War on Cancer", Bio/technology, 12, 320 (1994).
Pober and Cotran, "What Can Be Learned From the Expression of Endothelial Adhesion Molecules in Tissues?", Laboratory Investigation, 64(3), 301-305 (1991).
Vitetta et al., "Redesigning Nature's Poisons to Create Anti-Tumor Reagents," Science, 238:1098-1104, 1987.
Burgess et al., "Possible Dissociation of the Heparin-Binding and Mitogenic Activities of Heparin-Binding (Acidic Fibroblast) Growth Factor-1 from Its Receptor-Biding Activities by Site-Directed Mutagenesis of a Single Lysine Residue," J. Cell Biol., 111:2129-2138, 1990.
Gillies and Wesolowski, "Antigen Binding and Biological Activities of Engineered Mutant Chimeric Antibodies with Human Tumor Specificities," Hum. Antibod. Hybridomas, 1(1):47-54, 1990.
Lapierre et al., "Three Distinct Classes of Regulatory Cytokines Control Endothelial Cell MHC Antigen Expression," J. Exp. Med., 167:794-804, 1988.
Lazar et al., "Transforming Growth Factor .alpha.: Mutation of Aspartic Acid 47 and Leucine 48 Results in Different Biological Activities," Mol. Cell Biol., 8(3):1247-1252, 1988.
Qian et al., "Human Periphal Blood Lymphocytes Targeted with Bispecific Antibodies Release Cytokines That Are Essential for Inhibiting Tumor Growth," J. Immunol. 146(9):3250-3256, 1991.
Tao and Morrison, "Studies of Aglycosylated Chimeric Mouse-Human IgG -Role of Carbohydrate in the Structure and Effector Functions Mediated by the Human IgG Constant Region," J. Immunol. 143(8):2595-2601, 1989.
Waldman, Thomas A., "Monoclonal Antibodies in Diagnosis and Therapy," Science, 252: 1657-1662, 1991.
Wen et al., "Effects of .gamma.-Interferon on Major Histocompatibility Complex Antigen Expression and Lymphocytic Infiltration in the 9L Gliosarcoma Brain Tumor Model: Implications for Strategies of Immunotherapy," J. Neuroimmunol., 36:57-68, 1992.
Burrows et al., "A Murine Model for Antibody-Directed Targeting of Vascular Endothelial Cells in Solid Tumors," Cancer Research, 52:5954-5962, Nov. 1992.
Burrows and Thorpe, "Targeting the Vasculature of Solid Tumors," Journal of Controlled Release, 28:195-202, Jan. 1994.
Clauss et al., "A Polypeptide Factor Produced by Fibrosarcoma Cells That Induces Endothelial Tissue Factor and Enhances the Procoagulant Response to Tumor Necrosis Factor/Cachetin," The Journal of Biological Chemistry, 265(12):7078-7083, Apr. 1990.
Thorpe and Burrows, "Antibody-Directed Targeting of the Vasculature of Solid Tumors," Breast Cancer Research and Treatment, 36(2):237-251, 1995.
Thorpe, et al., International Symposium on Angiogensis, Mar. 1991.
Buring et al., "Endoglin is expressed on a subpopulation of immature erythroid cells of normal human bone marrow," Leukemia, 5(10):841-847, 1991.
Dvorak et al., "Structure of Solid Tumors and Their Vasculature: Implications for Therapy with Monoclonal Antibodies," Cancer Cells, 3(3):77-85, 1991.
Gougos & Letarte, "Primary Structure of Endoglin, an RGD-containing Glycoprotein of Human Endothelial Cells," The Journal of Biological Chemistry, 265(15):8361-8364, 1990.

Osborn et al., "Leukocyte Adhesion to Endothelium in Inflammation," Cell, 62:3-6, 1990.
June et al., "Role of the CD28 Receptor in T-Cell Activation," Immunology Today, 11(6):211-216, 1990.
Denekamp, "Vascular Attack as a Therapeutic Strategy for Cancer," Cancer and Metastasis Reviews, 9:267-282, 1990.
Scott et al., "Anti-CD3 Antibody Induces Rapid Expression of Cytokine Genes In Vivo," The Journal of Immunology, 145(7):2183-2188, 1990.
O'Connell & Edidin, "A Mouse Lymphoid Endothelial Cell Line Immortalized by Simian Virus 40 Binds Lymphocytes and Retains Functional Characteristics of Normal Endothelial Cells," The Journal of Immunology, 144(2):521-525, 1990.
Ledbetter et al., "CD 28 Ligation in T-Cell Activation: Evidence for Two Signal Transduction," Abstract only, Blood, 75(7):1531-1539, 1990.
Watanabe et al., "Exogenous Expression of Mouse Interferon .gamma. cDNA in Mouse Neuroblastoma C1300 Cells Results in Reduced Tumorigenicity by Augmented Anti-Tumor Immunity," Proceedings of the National Academy of Scientists, 86:9456-9460, 1989.
Schutt et al., "Human Monocyte Activation Induced by an Anti-CD14 Monoclonal Antibody," Immunology Letters, 19:321-328, 1988.
Thorpe et al., "Improved Antitumor Effects of Immunotoxins Prepared with Deglycosylated Ricin A-Chain and Hindered Disulfide Linkages," Cancer Research, 48:6396-6403, 1988.
Glennie et al., "Preparation and Performance of Bispecific (F(ab'.gamma.).sub.2 Antibody Containing Thioether-Linked Fab'.gamma. Fragments," The Journal of Immunology, 139(7):2367-2375, 1987.
Bevilacqua et al., "Identification of an Inducible Endothelial-Leukocyte Adhesion Molecule," Proceedings of the National Academy of Scientists, 84:9238-9242, 1987.
Cotran et al., "Induction and Detection of a Human Endothelial Activation Antigen In Vivo," Abstract only, The Journal of Experimental Medicine, 164(2):661-666, 1986.
Groenewegen et al., "Lymphokine Dependence of In Vivo Expression of MHC Class II Antigens by Endothelium," Nature, 316:361-263, 1985.
Moretta et al., Abstract only, The Journal of Experimental Medicine, 162(3):823-838, 1985.
Vaickus & Foon, "Overview of Monoclonal Antibodies in the Diagnosis and Therapy of Cancer," Cancer Investigation, 93(2):295-209, 1991.
Hagemier et al., "A Monoclonal Antibody Reacting with Endothelial Cells Of Budding Vessels in Tumors and Inflammatory Tissues, and Non-Reactive with Normal Adult Tissues," International Journal of Cancer, 38:481-488, 1986.
Duijvestijn et al., "Lymphoid Tissue-and Inflammation-Specific Endothelial Cell Differentiation defined by Monoclonal Antibodies," The Journal of Immunology, 138(3):713-719, 1987.
Murray et al., "Vascular Markers for Murine Tumours," Radiotherapy and Oncology, 16:221-234, 1989.
Schlingemann et al., "Monoclonal Antibody PAL-E Specific for Endothelium," Laboratory Investigation, 52(1):71-76, 1985.
Bruland et al., "New Monoclonal Antibodies Specific for Human Sarcomas," International Journal of Cancer, 38:27-31, 1986.
Reisfeld et al., "Human Tumor-Associated Antigens Defined by Monoclonal Antibodies," CRC Critical Reviews in Immunology, 5(1):27-53, 1984.
Schlom et al., "Monoclonal Antibodies Reactive with Breast Tumor-Assocatied Antigens," Advances in Cancer Research, 43:143-173, 1985.
Kaplan, "The Diagnostic and Therapeutic Use of Monoclonal Antibodies in Colorectal Cancer," Hematology/Oncology Clinics of North American, 3(1):125-134, 1989.
Smith & Teng, "Clinical Applications of Monoclonal Antibodies in Gynecologic Oncology," Cancer, 60:2068-2074, 1987.
Stavrou, "Monoclonal Antibodies in Neuro-Oncology," Neurosurgery Review, 13:7-18, 1990.
Shepard et al., "Monoclonal Antibody Therapy of Human Cancer: Taking the HEr2 Protooncogene to the Clinic," Journal of Clinical Immunology, 11(3):117-127, 1991.
Szymendera, "Clinical Usefulness of Three Monoclonal Antibody-Defined Tumor Markers: CA 19-9, CA 50, and CA 125," Tumour Biology, 7:333-342, 1986.

Catane & Longo, "Monoclonal Antibodies for Cancer Therapy," Isreal Journal of Medical Sciences, 24:471-476, 1988.
Greiner et al., "Applications of Monoclonal Antibodies and Recombinant Cytokines for the Treatment of Human Colorectal and Other Carcinomas," Journal of Surgical Oncology Supplement, 2:9-13, 1991.
Thor & Edgerton, "Monoclonal Antibodies Reactive with Human Breast or Ovarian Carcinoma: In Vivo Applications," Seminars in Nuclear Medicine, 19(4):295-308, 1989.
Thorpe et al., "Selective Killing of Proliferating Vascular Endothelial Cells by an Anti-Fibronectin Receptor Immunotoxin," 16th LH Gray Conference, University of Manchester Institute of Science and Technology, Sep. 17-21, 1990.
Ghose, Tarun I. et al., "Preparation of Antibody-Linked Cytotoxic Agents," Methods in Enzymology, 93:280-333, 1983.
Knowles, Phillip P. and Thorpe, Philip E., "Purification of Immunotoxins Containing Ricin A-Chain and Arbin A-Chain Using Blue Sepharose Cl-6B," Analytical Biochemistry, 160:440-443, 1987.
Wang, Theodore S.T. et al., "Photoreactive In-Cyclodextrin Inclusion Complex: a New Heterobifuntional Reagent for Antibody Labeling," Nuclear Medicine and Biology, 19(8):897-902, 1992.
PCT Search Report mailed Jun. 25, 1993.
Alvarez, J.A. et al., "Localization of Basic Fibroblast Growth Factor and Vascular Endothelial Growth Factor in Human Glial Neoplasms," Modern Pathology, 5(3):303-307, 1992.
Brown, Lawrence F. et al., "Expression of Vascular Permeability Factor (Vascular Endothelial Growth Factor) and Its Receptors in Adenocarcinomas of the Gastrointestinal Tract," Cancer Research, 53:4727-4735, 1993.
Kim, K. Jin et al., "Inhibition of vascular endothelial growth factor-induced angiogeneis suppresses tumor growth in vivo," Nature, 362:841-843, 1993.
Dvorak, Harold F. et al., "Distribution of Vascular Permeability Factor (Vascular Endothelial Growth Factor) in Tumors: Concentration in Tumor Blood Vessels," J. Exp. Med., 174:1275-1278, 1991.
Gerlach, Herwig et al., "Enhanced Responsiveness of Endothelium in the Growing/Motile State to Tumor Necrosis Factor/Cachectin," J. Exp. Med., 170:913-931, 1989.
Gougos, Anne et al., "Identification of distinct epitopes of endoglin, an RGD-containing glycoprotein of endothelial cells, leukemic cells, and syncytiotrophoblasts," International Immunology, 4(1):83-92, 1991.
Gougos, Anne et al., "Identification of a Human Endothelial Cell Antigen with Monoclonal Antibody 44G4 Produced Against a Pre-B Leukemic Cell Line," The Journal of Immunology, 141:1925-1933, 1988.
Gougos, Anne et al., "Biochemical Characterization of the 44G4 Antigen from the Hoon Pre-B Leukemic Cell Line," The Journal of Immunology, 141:1934-1940, 1988.
Jakeman, Lyn B. et al., "Binding Sites for Vascular Endothelial Growth Factor Are Localized on Endothelial Cells in Adult Rat Tissues," J. Clin. Invest., 89:244-253, 1993.
Nabel, Elizabeth G. et al., "Recombinant fibroblast growth factor-1 promotes intimal hyperplasia and angiogenesis in arteries in vivo," Nature, 362:844, 1993.
O'Connell, P.J. et al., "Endoglin: a 180-kD endothelial cell and macrophage restricted differentiation molecule," Clin. Exp. Immunol., 90:154-159, 1992.
Plate, K.H. et al., "Up-Regulation of Vascular Endothelial Growth Factor and Its Cognate Receptors in a Rat Glioma Model of Tumor Angiogenesis," Cancer Research, 53(23):5822-5827, 1993.

ART-UNIT: 166
PRIMARY-EXAMINER: Kight; John
ASSISTANT-EXAMINER: Hartley; Michael G.
ATTY-AGENT-FIRM: Arnold, White & Durkee

ABSTRACT:

The present invention relates generally to methods and compositions for targeting the vasculature of solid tumors using immunological- and growth factor-based reagents. In particular aspects, antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature of solid tumor masses through

recognition of tumor vasculature-associated antigens, such as, for example, through endoglin binding, or through the specific induction of endothelial cell surface antigens on vascular endothelial cells in solid tumors.

16 Claims, 0 Drawing figures

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 5919643 A

L10: Entry 6 of 11 File: USPT Jul 6, 1999

US-PAT-NO: 5919643
DOCUMENT-IDENTIFIER: US 5919643 A

TITLE: Methods and compositions for the use of apurinic/apyrimidinic endonucleases

DATE-ISSUED: July 6, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kelley; Mark R.	Zionsville	IN		
Duguid; John	Brownsburg	IN		
Eble; John	Indianapolis	IN		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Advanced Research & Technology Institute	Bloomington	IN			02

APPL-NO: 8/ 872719
DATE FILED: June 11, 1997

PARENT-CASE:
This application in is a continuation-in-part of U.S. Provisional Patent Application No. 60/019,561, filed Jun. 11, 1996 and U.S. Provisional Patent Application No. 60/019,602, filed Jun. 11, 1996. The entire text of each of the above-referenced disclosures is specifically incorporated by reference herein without disclaimer.

INT-CL: [6] C12Q 1/44, C12N 9/22
US-CL-ISSUED: 435/19; 435/199
US-CL-CURRENT: 435/19; 435/199
FIELD-OF-SEARCH: 435/19, 435/199

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4618585	October 1986	Chan	435/240
4633886	January 1987	Bucaro, Jr.	128/749
4666845	May 1987	Mattes et al.	435/240
4862899	September 1989	Bucaro	128/749
5171666	December 1992	Gutowski et al.	530/387.3
5306811	April 1994	Duffy	530/412
5320956	June 1994	Willingham et al.	435/172.2
5330972	July 1994	Cope	514/2
5360893	November 1994	Owens et al.	530/350
5399586	March 1995	Davies et al.	514/448
5403717	April 1995	Holmes	435/7.25

OTHER PUBLICATIONS

Ali et al., "Heterogeneity of subcellular localization of p53 protein in human glioblastomas," Cancer Res., 54:1-5, 1994.
Bamford, et al. "An immunohistochemical study of the distribution of epithelial antigens in the uterine cervix," Obstetrics & Gynecology, 61(5):603-608,. 1983.
Battaglia et al., "Immunosuppressive acidic protein (IAP) and squamous cell carcinoma antigen (SCC) in patients with cervical cancer," Gynecol. Oncol., 53:176-182, 1994.
Bosari et al., "Cytoplasmic accumulation of p53 protein: an independent prognostic indicator in colorectal adenocarcinomas," J. Nat'l. Cancer Instit., 86(9):681-687, 1994.
Bychkov et al., "Immunocytochemical localization of carcinoembryonic antigen (CEA), alphafetoprotein (AFP) and Human chorionic gonadotropin (HCG) in cervical neoplasia," Am. J. Clin. Pathol., 79(4):414-420, 1983.
Demple et al., "Cloning and expression of APE, the cDNA encoding the major human apurinic endonuclease: Definition of a family of DNA repair enzymes," Biochem., 88:11450-11454, 1991.
Duguid et al., "Differential cellular and subcellular expression of the human multifunctional apurinic/apyrimidinic endonuclease (APE/ref-1) DNA repair enzyme," Cancer Res., 55:6097-6102, 1995.
Duk et al., "Cancer of the uterine cervix: Sensitivity and specificity of serum squamous cell carcinoma antigen determinations," Gynecol. Oncol., 39:186-194, 1990.
Emanuele et al., "In vivo effect of ethanol on release of LH-releasing hormone and LH in rats," J. Endocrinol., 121:37-41, 1989.
Emanuele et al., "In vivo effects of acute EtOH on rat .alpha. and .beta. luteinizing hormone gene expression," Alcohol, 8:345-348, 1991.
Emanuele et al., "The effect of acute in vivo ethanol exposure on follicle stimulating hormone transcription and translation," Alcohol Clin. Exp. Res., 16(4):776-780, 1992.
Emanuele et al., "The effect of `binge` ethanol exposure on growth hormone and prolactin gene expression and secretion," Endocrinol., 131(5):2077-2082, 1992.
Gocze et al., "Serum levels of squamous cell carcinoma antigen and ovarian carcinoma antigen (CA 125) in patients with benign and malignant diseases of the uterine cervix," Oncol., 51:430-434, 1994.
Hale et al., "Prognostic value of epidermal growth factor receptor expression in cervical carcinoma," J. Clin. Pathol., 46:149-153, 1993.
Henner et al., "Purification and amino-terminal amino acid sequence of an apurinic/apyrimidinic endonuclease from calf thymus," Nucl. Acids Res., 15(14):5529-5544, 1987.
Hughes-Davies et al., "Expression of the human apurinic endonuclease gene (APE) in normal and malignant tissues," Int'l. J. Oncol., 6:749-752, 1995.
International Search Report dated Nov. 11, 1997 (PCT/US97/10078) (INDY:012P).
Kainz et al., "Cytokeratin subunit 19 measured by CYFRA21-1 assay in follow-up of cervical cancer," Gynecol. Oncol., 56:402-405, 1995.
Kelley et al., "Cross-reaction of albumin with polyclonal LH antibody on western blots," Endo. Res., 16(4);477-491, 1990.
Lam et al., "Evaluation of carcinoembryonic antigen, tissue polypeptide antigen,

and squamous cell carcinoma antigen in the detection of cervical cancers," Chinese Med. J., 50(1):7-13, 1992.
Lehtovirta et al., "Comparison between squamous cell carcinoma-associated antigen and CA-125 in patients with carcinoma of the cervix," Gynecol. Oncol., 37:276-278, 1990.
McDicken and Rainey, "The immunohistological demonstration of carcinoembryonic antigen in intra-epithelial and invasive squamous carcinoma of the cervix," Histopathol., 7:475-485, 1983.
Moll et al., "Two distinct mechanisms alter p53 in breast cancer: Mutation and nuclear exclusion," Proc. Natl. Acad. Sci. USA, 89:7262-7266, 1992.
Moll et al., "Wild-type p53 protein undergoes cytoplasmic sequestration in undifferentiated neuroblastomas but not in differentiated tumors," Proc. Natl. Acad. Sci. USA, 92:4407-4411, 1995.
Nam et al., "Urinary gonadotropin fragment, a new tumor marker," Gynecol. Oncol., 38:66-70, 1990.
Pectasides et al., "Squamous cell carcinoma antigen, tumor-associated trypsin inhibitor, and carcinoembryonic antigen for monitoring cervical cancer," Am. J. Clin. Oncol., 17(4):307-312, 1994.
Robertson et al., "Down-regulation of apurinic/apyrimidinic endonuclease expression is associated with the induction of apoptosis in differentiating myeloid leukemia cells," Cell Growth Diff., 8:443-449, 1997.
Rutanen et al., "Carcinoembryonic antigen in malignant and nonmalignant gynecologic tumors: Circulating levels and tissue localization," Cancer, 42:581-590, 1978.
Silber et al., "DNA polymerase .beta., apurinic/apyrimidinic endonuclease and O.sup.6 -methylguanine-DNA methyltransferase activity in brain tumors and adjacent normal brain," Proc. Am. Assoc. Cancer Res. Ann. Mtg, 36:550, Abstract #3275, 1995.
Stenmark-Askmalm et al., "Cellular accumulation of p53 protein: an independent prognostic factor in stage II breast cancer," Eur. J. Cancer, 30A(2):175-180, 1994.
Takahashi and Suzuki, "DNA synthesis-associated nuclear exclusion of p53 in normal human breast epithelial cells in culture," Oncogene, 9(1):183-188, 1994.
Toki and Yajima, "Immunohistochemical localization of carcinoembryonic antigen (CEA) in squamous cell carcinoma of the uterine cervix: Prognostic significance of localization pattern of CEA," Tohoku J. Exp. Med., 165:25-32, 1991.
van Nagell et al., "Carcinoembryonic antigen in carcinoma of the uterine cervix: Antigen distribution in primary and metastatic tumors," Cancer, 49:379-383, 1982.
Verlooy et al., "Clinical significance of squamous cell carcinoma antigen in cancer of the human uterine cervix," Gynecol. Obstet. Invest., 32:55-58, 1991.
Xu et al., "The apurinic/apyrimidinic endonuclease (APE/ref-1) DNA repair enzyme is elevated in premalignant and malignant cervical cancer," Anticancer Res., 17(5):1-7, 1997.
Yao et al., "Apoptosis in human adenocarcinoma HT29 cells induced by exposure to hypoxia," J. Nat'l. Cancer Instit., 87(2):117-122, 1995.
Zerrahn et al., "Correlation between the conformational phenotype of p53 and its subcellular location," Oncogene, 7(7):1371-1381, 1992.

ART-UNIT: 162
PRIMARY-EXAMINER: Patterson, Jr.; Charles L.
ATTY-AGENT-FIRM: Arnold, White & Durkee

ABSTRACT:

Disclosed are methods and compositions for identifying, monitoring and treating premalignant and malignant conditions in a human subject. The present invention further discloses methods and compositions for determining cells undergoing apoptosis, and for increasing the efficacy of a cancer therapy. The methods involve the use of apurinic/apyrimidinic endonuclease (APE), independently, as a marker for (pre)malignant conditions and for apoptosis. Also described are polyclonal antibody preparations for use in methods for detecting APE and methods for modulating expression susceptibility of cells to apoptosis.

15 Claims, 57 Drawing figures

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

☐ 7. Document ID: US 5863538 A

L10: Entry 7 of 11 File: USPT Jan 26, 1999

US-PAT-NO: 5863538
DOCUMENT-IDENTIFIER: US 5863538 A

TITLE: Compositions for targeting the vasculature of solid tumors

DATE-ISSUED: January 26, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thorpe; Philip E.	Dallas	TX		
Burrows; Francis J.	San Diego	CA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Board of Regents, The University of Texas System	Austin	TX			02

APPL-NO: 8/ 457487
DATE FILED: June 1, 1995

PARENT-CASE:
The present application is a division of copending application Ser. No. 08/350,212, filed Dec. 5, 1994, which is a continuation-in-part of U.S. patent application Ser. No. 08/205,330, filed Mar. 2, 1994 now U.S. Pat. No. 5,855,866; which is a continuation-in-part of U.S. patent application Ser. No. 07/846,349, filed Mar. 05, 1992 (now abandoned). The entire text and figures of which disclosures are specifically incorporated by reference herein without disclaimer.

INT-CL: [6] A61K 39/395, C12P 21/08, C07K 16/00
US-CL-ISSUED: 424/136.1; 424/138.1, 424/141.1, 424/154.1, 424/155.1, 424/172.1, 424/173.1, 424/174.1, 424/181.1, 530/388.22, 530/387.7, 530/387.3
US-CL-CURRENT: 424/136.1; 424/138.1, 424/141.1, 424/154.1, 424/155.1, 424/172.1, 424/173.1, 424/174.1, 424/181.1, 530/387.3, 530/387.7, 530/388.22
FIELD-OF-SEARCH: 424/136.1, 424/138.1, 424/141.1, 424/154.1, 424/155.1, 424/172.1, 424/173.1, 424/174.1, 424/181.1, 530/387.3, 530/387.7, 530/388.22

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4456550	June 1984	Dvorak et al.	260/112R
4472509	September 1984	Gansow et al.	N/A
4536387	August 1985	Sakamoto et al.	424/14
5021236	June 1991	Gries et al.	N/A
5081034	January 1992	Bevilacqua et al.	N/A
5342757	August 1994	Garin-Chesa et al.	435/7.21
5399346	March 1995	Anderson et al.	424/93.21
5403713	April 1995	Bevilacqua et al.	435/7.1
5632991	May 1997	Gimbrone, Jr.	424/178.1

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 81/01145	April 1981	WOX	
WO 90/03801	April 1990	WOX	
WO 90/05539	May 1990	WOX	
WO 90/13300	November 1990	WOX	
WO 90/12585	November 1990	WOX	
WO 92/12729	August 1992	WOX	
WO 92/19646	November 1992	WOX	
WO 93/08210	April 1993	WOX	
WO 93/08473	April 1993	WOX	
WO 93/17715	September 1993	WOX	
WO 94/05328	March 1994	WOX	
WO 94/10202	May 1994	WOX	
WO 94/11499	May 1994	WOX	

OTHER PUBLICATIONS

Osborn et al., "Leukocyte Adhesion to Endothelium in Inflammation," Cell, 62:3-6, 1990.
June et al., "Role of the CD28 Receptor in T-Cell Activation," Immunology Today, 11(6):211-216, 1990.
Denekamp, "Vascular Attack as a Therapeutic Strategy for Cancer," Cancer and Metastasis Reviews, 9:267-282, 1990.
Scott et al., "Anti-CD3 Antibody Induces Rapid Expression of Cytokine Genes In Vivo," The Journal of Immunology, 145(7):2183-2188, 1990.
O'Connell & Edidin, "A Mouse Lymphoid Endothelial Cell Line Immortalized by Simian Virus 40 Binds Lymphocytes and Retains Functional Characteristics of Normal Endothelial Cells," The Journal of Immunology, 144(2):521-525, 1990.
Ledbetter et al., "CD 28 Ligation in T-Cell Activation: Evidence for Two Signal Transduction," Abstract only, Blood, 75(7):1531-1539, 1990.
Watanabe et al., "Exogenous Expression of Mouse Interferon .gamma. cDNA in Mouse Neuroblastoma C1300 Cells Results in Reduced Tumorigenicity by Augmented Anti-Tumor Immunity," Proceedings of the National Academy of Scientists, 86:9456-9460, 1989.
Schutt et al., "Human Monocyte Activation Induced by an Anti-CD14 Monoclonal Antibody," Immunology Letters, 19:321-328, 1988.
Thorpe et al., "Improved Antitumor Effects of Immunotoxins Prepared with Deglycosylated Ricin A-Chain and Hindered Disulfide Linkages," Cancer Research, 48:6396-6403, 1988.
Glennie et al., "Preparation and Performance of Bispecific (F(ab'.gamma.).sub.2 Antibody Containing Thioether-Linked Fab'.gamma. Fragments," The Journal of Immunology, 139(7):2367-2375, 1987.
Bevilacqua et al., "Identification of an Inducible Endothelial-Leukocyte Adhesion Molecule," Proceedings of the National Academy of Scientists,

84:9238-9242, 1987.
Cotran et al., "Induction and Detection of a Human Endothelial Activation Antigen In Vivo," Abstract only, The Journal of Experimental Medicine, 164(2):661-666, 1986.
Groenewegen et al., "Lymphokine Dependence of In Vivo Expression of MHC Class II Antigens by Endothelium," Nature, 316:361-263, 1985.
Moretta et al., Abstract only, The Journal of Experimental Medicine, 162(3):823-838, 1985.
Vaickus & Foon, "Overview of Monoclonal Antibodies in the Diagnosis and Therapy of Cancer," Cancer Investigation, 93(2):295-209, 1991.
Hagemeier et al., "A Monoclonal Antibody Reacting with Endothelial Cells of Budding Vessels in Tumors and Inflammatory Tissues, and Non-Reactive with Normal Adult Tissues," International Journal of Cancer, 38:481-488, 1986.
Duijvestijn et al., "Lymphoid Tissue- and Inflammation-Specific Endothelial Cell Differentiation defined by Monoclonal Antibodies," The Journal of Immunology, 138(3):713-719, 1987.
Murray et al., "Vascular Markers for Murine Tumours," Radiotherapy and Oncology, 16:221-234, 1989.
Schlingemann et al., "Monoclonal Antibody PAL-E Specific for Endothelium," Laboratory Investigation, 52(1):71-76, 1985.
Bruland et al., "New Monoclonal Antibodies Specific for Human Sarcomas," International Journal of Cancer, 38:27-31, 1986.
Reisfield et al., "Human Tumor-Associated Antigens Defined by Monoclonal Antibodies," CRC Critical Reviews in Immunology, 5(1):27-53, 1984.
Schlom et al., "Monoclonal Antibodies Reactive with Breast Tumor-Associated Antigens," Advances in Cancer Research, 43:143-173, 1985.
Kaplan, "The Diagnostic and Therapeutic Use of Monoclonal Antibodies in Colorectal Cancer," Hematology/Oncology Clinics of North American, 3(1):125-134, 1989.
Smith & Teng, "Clinical Applications of Monoclonal Antibodies in Gynecologic Onocology ," Cancer, 60:2068-2074, 1987.
Stavrou, "Monoclonal Antibodies in Neuro-Oncology," Neurosurgery Review, 13:7-18, 1990.
Shepard et al., "Monoclonal Antibody Therapy of Human Cancer: Taking the HEr2 Protoonocgene to the Clinic," Journal of Clinical Immunology, 11(3):117-127, 1991.
Szymendera, "Clinical Usefulness of Three Monoclonal Antibody-Defined Tumor Markers: CA 19-9, CA 50, and CA 125," Tumour Biology, 7:333-342, 1986.
Catane & Longo, "Monoclonal Antibodies for Cancer Therapy," Israel Journal of Medical Sciences, 24:471-476, 1988.
Greiner et al., "Applications of Monoclonal Antibodies and Recombinant Cytokines for the Treatment of Human Colorectal and Other Carcinomas," Journal of Surgical Oncology Supplement, 2:9-13, 1991.
Thor & Edgerton, "Monoclonal Antibodies Reactive with Human Breast or Ovarian Carcinoma: In Vivo Applications," Seminars in Nuclear Medicine, 19(4):295-308, 1989.
Thorpe et al., "Selective Killing of Proliferating Vascular Endothelial Cells by an Anti-Fibronectin Receptor Immunotoxin," 16th LH Gray Conference, University of Manchester Insitute of Science and Technology, Sep. 17-21, 1990.
Thorpe et al., "Targeting To Proliferating Vascular Endothelium," International Symposium on Angiogenesis, St. Gallen, Switzerland, Abstract, Mar. 13-15, 1991.
Ghose, Tarun I. et al., "Preparation of Antibody-Linked Cytotoxic Agents," Methods in Enzymology, 93:280-333, 1983.
Knowles, Phillip P. and Thorpe, Philip E., "Purification of Immunotoxins Containing Ricin-A-Chain and Abrin A-Chain Using Blue Sepharose CL-6B," Analytical Biochemistry, 160:440-443, 1987.
Wang, Theodore S.T. et al., "Photoreactive In-Cyclodextrin Inclusion Complex: a New Heterobifunctional Reagent for Antibody Labeling," Nuclear Medicine and Biology, 19(8):897-902, 1992.
Alvarez, J.A. et al., "Localization of Basic Fibroblast Growth Factor and Vascular Endothelial Growth Factor in Human Glial Neoplasms," Modern Pathology, 5(3):303-307, 1992.
Brown, Lawrence F. et al., "Expression of Vascular Permeability Factor (Vascular Endothelial Growth Factor) and Its Receptors in Adenocarcinomas of the Gastrointestinal Tract," Cancer Research, 53:4727-4735, 1993.

Kim, K. Jin et al., "Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumor growth in vivo," Nature, 362:841-843, 1993.
Dvorak, Harold F. et al., "Distribution of Vascular Permeability Factor (Vascular Endothelial Growth Factor) in Tumors: Concentration in Tumor Blood Vessels," J. Exp. Med., 174:1275-1278, 1991.
Gerlach, Herwig et al., "Enhanced Responsiveness of Endothelium in the Growing/Motile State to Tumor Necrosis Factor/Cachetin," J. Exp. Med., 170:913-931, 1989.
Gougos, Anne et al., "Identification of distinct epitopes of endoglin, an RGD-containing glycoprotein of endothelial cells, leukemic cells, and syncytiotrophoblasts," International Immunology, 4(1):83-92, 1991.
Gougos, Anne et al., "Identification of a Human Endothelial Cell Antigen with Monoclonal Antibody 44G4 Produced Against a Pre-B Leukemic Cell Line," The Journal of Immunology, 141:1925-1933, 1988.
Gougos, Anne et al., "Biochemical Characterization of the 44G4 Antigen from the Hoon Pre-B Leukemic Cell Line," The Journal of Immunology, 141:1934-1940, 1988.
Hagemeier, Hans-Hermann et al., "A Monoclonal Antibody Reacting with Endothelial Cells of Budding Vessels in Tumors and Inflammatory Tissues, and Non-Reactive with Normal Adult Tissues," Int. J. Cancer, 38:481-488, 1986.
Jakeman, Lyn B. et al., "Binding Sites for Vascular Endothelial Growth Factor Are Localized on Endothelial Cells in Adult Rat Tissues," J. Clin. Invest., 89:244-243, 1992.
Nabel, Elizabeth G. et al., "Recombinant fibroblast growth factor-1 promotes intimal hyperplasia and angiogenesis in arteries in vivo," Nature, 362:844, 1993.
O'Connell, P.J. et al., "Endoglin: a 180-kD endothelial cell and macrophage restricted differentiation molecule," Clin. Exp. Immunol., 90:154-159, 1992.
Plate, K.H. et al., "Up-Regulation of Vascular Endothelial Growth Factor and Its Cognate Receptors in a Rat Glioma Model of Tumor Angiogenesis," Cancer Research, 53(23):5822-5827, 1993.
Plate, Karl H. et al., "Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo," Nature, 359:845-848, 1992.
Rettig, Wolfgang J. et al., "Identification of endosialin, a cell surface glycoprotein of vascular endothelial cells in human cancer," Proc. Natl. Acad. Sci. USA, 89:10832-10836, 1992.
Sarma, Vidya et al., "Cloning of a Novel Tumor Necrosis Factor-.alpha.-Inducible Primary Response Gene that is Differentially Expressed in Development and Capillary Tube-Like Formation in vitro," The Journal of Immunology, 148:3302-3312, 1992.
Senger, Donald R. et al., "Vascular permeability factor (VPF, VEGF) in tumor biology," Cancer and Metatasts Reviews, 12:303-324, 1993.
Shweiki, Dorit et al., "Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis," Nature, 359:843-845, 1992.
Wang, J.M. et al., "A Monoclonal Antibody Detects Heterogeneity in Vascular Endothelium of Tumours and Normal Tissues," Int. J. Cancer, 54:363-370, 1993.
Westphal, Johan R. et al., "A New 180-kDa Dermal Endothelial Cell Activation Antigen: In Vitro and In Situ Characteristics," The Journal of Investigative Dermatology, 100(1):27-34, 1993.
Yeo, Kiang-Teck et al., "Vascular Permeability Factor (Vascular Endothelial Growth Factor) in Guinea Pig and Human Tumor and Inflammatory Effusions," Cancer Research, 53:2912-2918, 1993.
Buring et al., "Endoglin is expressed on a subpopulation of immature erythroid cells of normal human bone marrow," Leukemia, 5(10):841-847, 1991.
Dvorak et al., "Structure of Solid Tumors and Their Vasculature: Implications for Therapy with Monoclonal Antibodies," Cancer Cells, 3(3):77-85, 1991.
Gougos & Letarte, "Primary Structure of Endoglin, an RGD-containing Glycoprotein of Human Endothelial Cells," The Journal of Biological Chemistry, 265(15):8361-8364, 1990.
Burrows et al., "A Murine Model for Antibody-Directed Targeting of Vascular Endothelial Cells in Solid Tumors," Cancer Research, 52:5954-5962, Nov. 1992.
Burrows and Thorpe, "Targeting the Vasculature of Solid Tumors," Journal of Controlled Release, 28:195-202, Jan. 1994.
Clauss et al., "A Polypeptide Factor Produced by Fibrosarcoma Cells That Induces Endothelial Tissue Factor and Enhances the Procoagulant Response to Tumor Necrosis Factor/Cachetin," The Journal of Biological Chemistry,

265(12):7078-7083, Apr. 1990.
Thorpe and Burrows, "Antibody-Directed Targeting of the Vasculature of Solid Tumors," Breast Cancer Research and Treatment, 36 (2) :237-251, 1995.
Yamazaki et al., "Bispecific Monoclonal Antibodies with Specificities for Activated Platelets and Thrombolytic Agents, Their Production and Use," Abstract for Canadian Patent Application CA 2039259; Chem Abstracts, 117(11), Abstract #109988.
International Search Report, Mailed Nov. 24, 1995.
Burgess et al., "Possible Dissociation of the Heparin-Binding and Mitogenic Activities of Heparin-Binding (Acidic Fibroblast) Growth Factor-1 from Its Receptor-Biding Activities by Site-Directed Mutagenesis of a Single Lysine Residue," J. Cell Biol., 111:2129-2138, 1990.
Gillies and Wesolowski, "Antigen Binding and Biological Activities of Engineered Mutant Chimeric Antibodies with Human Tumor Specificities," Hum. Antibod. Hybridomas, 1(1):47-54, 1990.
Lapierre et al., "Three Distinct Classes of Regulatory Cytokines Control Endothelial Cell MHC Antigen Expression," J. Exp. Med., 167:794-804, 1988.
Lazar et al., "Transforming Growth Factor .alpha.: Mutation of Aspartic Acid 47 and Leucine 48 Results in Different Biological Activities," Mol. Cell Biol., 8(3):1247-1252, 1988.
Qian et al., "Human Peripheral Blood Lymphocytes Targeted with Bispecific Antibodies Release Cytokines That Are Essential for Inhibiting Tumor Growth," J. Immunol., 146(9):3250-3256, 1991.
Tao and Morrison, "Studies of Aglycosylated Chimeric Mouse-Human IgG--Role of Carbohydrate in the Structure and Effector Functions Mediated by the Human IgG Constant Region," J. Immunol., 143(8):2595-2601, 1989.
Waldman, Thomas A., "Monoclonal Antibodies in Diagnosis and Therapy," Science, 252:1657-1662, 1991.
Wen et al., "Effects of .gamma.-Interferon on Major Histocompatibility Complex Antigen Expression and Lymphocytic Infiltration in the 9L Gliosarcoma Brain Tumor Model: Implications for Strategies of Immunotherapy," J. Neuroimmunol., 36:57-68, 1992.
Vietta et al., "Redesigning Nature's Poisons to Create Anti-Tumor Reagents," Science, 228:1098-1104, 1987.
Songsivilai & Lachmann, "Bispecifc antibody: a tool for diagnosis and treatment of disease", Clin. exp. Immunol., 79, 315-321 (1990).
Dermer, "Another Anniversary for the War on Cancer", Bio/technology, 12, 320 (1994).
Pober and Cotran, "What Can Be Learned From the Expression of Endothelial Adhesion Molecules in Tissues?", Laboratory Investigation, 64(3), 301-305 (1991).
Aoyagi, "Distribution of Plasma Fibronectin in the Metastatic Lesions of Cancer: Experimental Study by Autoradiography," Thrombosis Research, 49:265-75, 1988.
Balza et al., "Production and Characterization of Monoclonal Antibodies Specific for Different Epitopes of Human Tenascin," FEBS 332(1,2):39-43, 1993.
Bjorndahl, et al., "Human T Cell Activation: Differential Response to Anti-CD28 As Compared to Anti-CD3 Monoclonal Antibodies," Eur. J. Immunol., 19:881-87, 1989.
Blanchard, et al., "Infiltration of Interleukin-2-Inducible Killer Cells in Ascitic Fluid and Pleural Effusions of Advanced Cancer Patients," Cancer Research, 48: 6321-27, 1988.
Bohlen, et al., "Cytolysis of Leukemic B-Cells by T-Cells Activated via Two Bispecific Antibodies," Cancer Research, 53:4310-14, 1993.
Borsi, et al., "Expression of Different Tenascin Isoforms in Normal, Hyperplastic and Neoplastic Human Breast Tissues," Int. J. Cancer, 52:688-92, 1992.
Boyer, et al., "Differential Induction by Interferons of Major Histocompatibility Complex-Encoded and Non-Major Histocompatibility Complex-Encoded Antigens in Human Breast and Ovarian Carcinoma Cell Lines," Cancer Research, 49:2928-34, 1989.
Burton-Wurster, et al., "Expression of the Ed B Fibronectin Isoform in Adult Human Articular Cartilage ," Biochemical and Biophysical Research Communication 165(2): 782-87, 1989.
Collins, et al., "Immune Interferon Activates Multiple Class II Major Histocompatibility Complex Genes and the Associated Invariant Chain Gene in

Human Endothelial Cells and Dermal Fibroblasts," Proc. Natl. Acad. Sci. USA, 81:4917-21, 1984.
Carnemolla et al., "A Tumor-associated Fibronectin Isoform Generated by Alternative Splicing of Messenger RNA Precursors," The Journal of Cell Biology, 108:1139-48, 1989.
Carnemolla et al., "The Inclusion of the Type III Repeat ED-B in the Fibronectin Molecule Generates Conformational Modifications that Unmask a Cryptic Sequence," The Journal of Biological Chemistry, 267(34):24589:92, 1992.
Carnemolla, et al., "Phage Antibodies with Pan-Species Recognition of the Oncofoetal Angiogenesis Marker Fibronectin ED-B Domain," Int. J. Cancer 68:397-405, 1996.
Castellani, et al., "The Fibronectin Isoform Containing the ED-B Oncofoetal Domain: A Marker of Angiogenesis," Int. J. Cancer, 59:612-18, 1994.
Conforti, et al., "Human Endothelial Cells Express Integrin Receptors on the Luminal Aspect of Their Membrane," Blood, 80(2):437-46, 1992.
Dillman, "Monoclonal Antibodies for Treating Cancer," Annals of Internal Medicine, 111(7) 592-600, 1989.
Farnoud, et al., "Fibronectin Isoforms Are Differentially Expressed in Normal and Adenomatous Human Anterior Pituitaries," Int. J. Cancer, 61:27-34, 1995.
Garin-Chesa, et al., "Cell Surface Glycoprotein of Reactive Stromal Fibroblasts As A Potential Antibody Target in Human Epithelial Cancers," Proc. Natl. Acad. Sci. USA, 87:7235-39, 1990.
Groenewegen, et al., "Lymphokine Dependence of In Vivo Expression of MHC Class II Antigens by Endothelium," Nature, 316:361-63, 1985.
Harris and Emery, "Therapeutic Antibodies--The Coming of Age," Btech, 11:42-44, 1993.
June, et al., "T-Cell Proliferation Involving the CD28 Pathway Is Associated with Cyclosporine-Resistant Interleukin 2 Gene Expression," Molecular and Cellular Biology 7(12):4473-81, 1987.
Kaczmarek, et al., "Distribution of Oncofetal Fibronectin Isoforms in Normal Hyperplastic and Neoplastic Human Breast Tissues," Int. J. Cancer, 58:11-16, 1994.
Koulova et al., "The CD28 Ligand B7/BB1 Provides Costimulatory Signal for Alloactivation of CD4.sup.+ T Cells," J. Exp. Med. 173:759-62, 1991.
Kurosawa, et al., "Early Appearance and Activation of Natural Killer Cells in Tumor-Infiltrating Lymphoid Cells During Tumor Development," Eur. J. Immunol. 23:1029-33, 1993.
Lampugnani, et al., "The Role of Integins in the Maintenance of Endothelial Monolayer Integrity," The Journal of Cell Biology, 112(3):479-90, 1991.
Linnala, et al., "Human Amnion Epithelial Cells Assemble Tenascins and Three Fibronectin Isoforms in the Extracellular Matrix," FEBS, 314(1,2):74-78, 1993.
Maeda, et al., "Production and Characterization of Tumor Infiltrating Lymphocyte Clones Derived from B16-F10 Murine Melanoma," The Journal of Investigative Dermatology 97(2):183-89, 1991.
Natali, et al., "Comparative Analysis of the Expression of the Extracellular Matrix Protein Tenascin in Normal Human Fetal, Adult and Tumor Tissues," Int. J. Cancer, 47:811-16, 1991.
Oyama, et al., "Coordinate Oncodevelopmental Modulation of Alternative Splicing of Fibronectin Pre-Messenger RNA at ED-A, ED-B and CS1 Regions in Human Liver Tumors," Cancer Research 53:2005-11, 1993.
Peters, et al., "Expression of the Alternatively Spliced EIIIB Segment of Fibronectin," Cell Adhesion and Communication, 3:67-89, 1995.
Pober et al., "Ia Expression by Vascular Endothelium Is Inducible by Activated T Cells and by Human .gamma. Interferon," J. Exp. Med. 157:1339-53, 1983.
Pohl, et al., "CD30-Antigen-Specific Targeting and Activation of T Cells via Murine Bispecific Monoclonal Antiodies Against CD3 and CD28: Potential Use for the Treatment of Hodgkin's Lymphoma," Int. J. Cancer, 54:820-27, 1993.
Renner, et al., "Cure of Xenografted Human Tumors by Bispecific Monoclonal Antibodies and Human T Cells," Science, 264:833-35, 1994.
Rettig, et al., "Cell-Surface Glycoproteins of Human Sarcomas: Differential Expression in Normal and Malignant Tissues and Cultured Cells," Proc. Natl. Acad. Sci. USA, 85:3110-14, 1988.
Rettig, et al., "Identification of Endosialin, A Cell Surface Glycoprotein of Vascular Endothelial Cells in Human Cancer," Proc. Natl. Acad. Sci. USA, 89:10832-36, 1992.

Rosenberg, Steven, "Lymphokine-Activated Killer Cells: A New Approach to Immunotherapy of Cancer," JNCI 75(4):595-603, 1985.
Rosenberg, et al., "Observations of the Systemic Administration of Autologous Lymphokine-Activated Killer Cells and Recombinant Interleukin-2 to Patients with Metastatic Cancer," The New England Journal of Medicine, 313(23):1485-92, 1985.
Ruiter, et al., "Monoclonal Antibody-Defined Human Endothelial Antigens as Vascular Markers," J. Investigative Dermatol., 93(2):25S-32S, 1989.
Saiki et al., "Anti-metastatic and Anti-invasive Effects of Polymeric Arg-Gly-Asp (RGD) Peptide, Poly(RGD), and Its Analogues," Jpn. J. Cancer Res. 81:660-67, 1990.
Saiki et al., "Inhibition of Tumor Angiogenesis by a Synthetic Cell-Adhesive Polypeptide Containing the Arg-Gly-Asp (RGD) Sequence of Fibronectin, Poly(RGD)," Jpn. J. Cancer Res. 81:668-75, 1990.
Schlingemann, et al., "Differential Expression of Markers for Endothelial Cells, Pericytes, and Basal Lamina in the Microvasculature of Tumors and Granulation Tissue," Am. J. Pathol., 138(6):1335-47, 1991.
Schwarzbauer, "Alternative Splicing of Fibronectin: Three Variants, Three Functions," BioEssays 13(10)527-33, 1991.
Siri, et al., "Human Tenascin: Primary Structure, Pre-mRNA Splicing Patterns and Localization of the Epitopes Recognized by Two Monclonal Antibodies," Nucleic Acids Research, 19(3):525-31, 1991.
Steiniger, et al., "Interferon-.gamma. in Vivo. Induction and Loss of Class II MHC Antigens and Immture Myelomonocytic Cells in Rat Organs," Eur. J. Immunol. 18:661-69, 1988.
Street, et al., "In Vivo Administration of Fab' Fragments of Anti-L3T4 (Gk1.5) Antibody Inhibits the T Helper Cell Function of Murine Lymph Node Cells," Cellular Immunology 120:75-81, 1989.
Thompson, et al., "CD28 Activation Pathway Regulates the Production of Multiple T-Cell-Derived Lymphokines/Cytokines," Proc. Natl. Acad. Sci. USA, 86:1333-37, 1989.
Ueda, et al., "Selective Distribution of Fibronectin to a Tumor-Cell Line," Cancer Letters 31:261-65, 1986.
Vartio, et al., "Differential Expression of the ED Sequence-Containing Form of Cellular Fibronectin in Embryonic and Adult Human Tissues," Journal of Cell Science, 88:419-30, 1987.
Welt, et al., "Phase I Localization Study of .sup.131 I-monoclonal Antibody F19 Detecting an Activation Antigen of Neoplastic Stroma," Proceedings of the American Association for Cancer Research, 33:319, 1992, Abstract No. 1900.
Werb, et al., "Signal Transduction through the Fibronectin Receptor Induces Collagenases and Stromelysin Gene Expression," The Journal of Cell Biology., 109:877-89, 1989.
Osband and Ross, "Problems in the Investigational Study and Clinical Use of Cancer Immunotherapy," Immunotherapy, 11:193-195, 1990.
Chatterjee, et al., "Idiotypic antibody immunotherapy of cancer," Cancer Immunol. Immunotherapy, 38:75-82, 1994.
Burrows et al., "Influence of Tumor-derived Interleukin 1 on Melanoma-Endothelial Cell Interactions in Vitro," Cancer Research, 51:4768-4775, Sep. 15, 1991.
European Application Serial No. 93 906 289.9 Office Action dated Sep. 25, 1997.
Wellicome et al., A Monoclonal Antibody That Detects A Novel On Endothelial Cells That Is Induced By Tumor Necrosis Factor, IL-1, Or Lipopolysaccharide, J. Immunol., 144(7):2558-2565, Apr. 1, 1990.
Pietersz et al. Adv. Immunol. 56:301-387, 1994.
Berzovsky et al. Fundamental Immunology, Raven Press, NY William E. Paul (ed.) Chapter 8, p. 242, 1993.

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ABSTRACT:

The present invention relates generally to methods and compositions for targeting the vasculature of solid tumors using immunological- and growth

factor-based reagents. In particular aspects, antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature of solid tumor masses through recognition of tumor vasculature-associated antigens, such as, for example, through endoglin binding, or through the specific induction of endothelial cell surface antigens on vascular endothelial cells in solid tumors.

23 Claims, 37 Drawing figures

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PARENT-CASE:
The present application is a continuation-in-part of U.S. patent application Ser. No. 07/846,349, filed Mar. 05, 1992, now abandoned. The entire text and figures of which disclosure is specifically incorporated by reference herein without disclaimer.

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U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4456550	June 1984	Dvorak et al.	260/112R
4472509	September 1984	Gansow et al.	436/548
4536387	August 1985	Sakamoto et al.	424/14
5021236	June 1991	Gries et al.	424/9
5081034	January 1992	Bevilacqua et al.	435/252.33
5342757	August 1994	Garin-Chesa et al.	435/7.21
5399346	March 1995	Anderson et al.	424/93.21
5403713	April 1995	Bevilacqua et al.	435/7.1
5632991	May 1997	Gimbrone, Jr.	424/178.1
5659013	August 1997	Senger et al.	530/350

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 81/01145	April 1981	WOX	
WO 90/03801	April 1990	WOX	
Wo 90/05539	May 1990	WOX	
WO 90/12585	November 1990	WOX	
Wo 90/13300	November 1990	WOX	
WO 92/12729	August 1992	WOX	
WO 92/19646	November 1992	WOX	
WO 93/08473	April 1993	WOX	
WO 93/08210	April 1993	WOX	
WO 93/177515	September 1993	WOX	
WO 94/05328	March 1994	WOX	
WO 94/11499	May 1994	WOX	
WO 94/10202	May 1994	WOX	

OTHER PUBLICATIONS

Burrows et al., "A Murine Model for Antibody-Directed Targeting of Vascular Endothelial Cells in Solid Tumors," Cancer Research, 52:5954-5962, Nov. 1992.
Burrows and Thorpe, "Targeting the Vasculature of Solid Tumors," Journal of Controlled Release, 28:195-202, Jan. 1994.
Clauss et al., "A Polypeptide Factor Produced by Fibrosarcoma Cells That Induces Endothelial Tissue Factor and Enhances the Procoagulant Response to Tumor Necrosis Factor/Cachetin," The Journal of Biological Chemistry, 265(12):7078-7083, Apr. 1990.
Thorpe and Burrows, "Antibody-Directed Targeting of the Vasculature of Solid Tumors," Breast Cancer Research and Treatment, 36(2):237-251, 1995.
Yamazaki et al., "Bispecific Monoclonal Antibodies with Specificities for Activated Platelets and Thrombolytic Agents, Their Production and Use," Abstract for Canadian Patent Application CA 2039259; Chem Abstracts, 117(11), Abstract #109988, 1995.
Buring et al., "Endoglin is expressed on a subpopulation of immature erythroid cells of normal human bone marrow," Leukemia, 5(10):841-847, 1991.
Dvorak et al., "Structure of Solid Tumors and Their Vasculature: Implications for Therapy with Monoclonal Antibodies," Cancer Cells, 3(3):77-85, 1991.
Gougos & Letarte, "Primary Structure of Endoglin, an RGD-containing Glycoprotein of Human Endothelial Cells," The Journal of Biological Chemistry, 265(15):8361-8364, 1990.
Introduction to Immunology, Kimball, pp. 64-68, 1990.
Osband and Ross, "Problems in the Investigational Study and Clinical Use of Cancer Immunotherapy," Immunotherapy, 11:193-195, 1990.
Chatterjee, et al., Idiotypic antibody immunotherapy of cancer, Cancer Immunol.

Immunotherapy, 38:75-82, 1994.
Burrows et al., "Influence of Tumor-derived Interleukin 1 on Melanoma-Endothelial Cell Interactions in Vitro," Cancer Research, 51:4768-4775, Sep. 15, 1991.
European Application Serial No. 93 906 289.9 Office Action dated Sep. 25, 1997.
Wellicome et al., A Monoclonal Antibody That Detects A Novel Antigen on Endothelial Cells That Is Induced By Tumor Necrosis Factor, IL-1, or Lipopolysaccharide, J. Immunol., 144(7):2558-2565, Apr. 1, 1990.
Aoyagi, "Distribution of Plasma Fibronectin in the Metastatic Lesion of Cancer: Experimental Study by Autoradiography," Thrombosis Research, 49:265-75, 1988.
Balza et al., "Production and Characterization of Monoclonal Antibodies Specific for Different Epitopes of Human Tenascin," FEBS 332(1,2):39-43, 1993.
Bjorndahl, et al., "Human T Cell Activation: Differential Response to Anti-CD28 As Compared to Anti-CD3 Monoclonal Antibodies," Eur. J. Immunol., 19:881-87, 1989.
Blanchard, et al., "Infiltration of Interleukin-2-Inducible Killer Cells in Ascitic Fluid and Pleural Effusions of Advanced Cancer Patients," Cancer Research, 48:6321-27, 1988.
Bohlen, et al., "Cytolysis of Leukemic B-Cells by T-Cells Activated via Two Bispecific Antibodies," Cancer Research, 53:4310-14, 1993.
Borsi, et al., "Expression of Different Tenascin Isoforms in Normal, Hyperplastic and Neoplastic Human Breast Tissues," Int. J. Cancer, 52:688-92, 1992.
Boyer, et al., "Differential Induction by Interferons of Major Histocompatibility Complex-Encoded and Non-Major Histocompatibility Complex-Encoded Antigens in Human Breast and Ovarian Carcinoma Cell Lines," Cancer Research, 49:2928-34, 1989.
Burton-Wurster, et al., "Expression of the Ed B Fibronectin Isoform in Adult Human Articular Cartilage," Biochemical and Biophysical Research Communication 165(2): 782-87, 1989.
Collins, et al., "Immune Interferon Activates Multiple Class II Major Histocompatibility Complex Genes and the Associated Invariant Chain Gene in Human Endothelial Cells and Dermal Fibroblasts," Proc. Natl. Acad. Sci. USA, 81:4917-21, 1984.
Carnemolla et al., "A Tumor-associated Fibronectin Isoform Generated by Alternative Splicing of Messenger RNA Precursors," The Journal of Cell Biology, 108:1139-48, 1989.
Carnemolla et al., "The Inclusion of the Type III Repeat ED-B in the Fibronectin Molecule Generates Conformational Modifications that Unmask a Cryptic Sequence," The Journal of Biological Chemistry, 267(34):24589:92, 1992.
Carnemolla, et al., "Phage Antibodies with Pan-Species Recognition of the Oncofoetal Angiogenesis Marker Fibronectin ED-B Domain," Int. J. Cancer 68:397-405, 1996.
Castellani, et al., "The Fibronectin Isoform Containing the ED-B Oncofoetal Domain: A Marker of Angiogenesis," Int. J. Cancer, 59:612-18, 1994.
Conforti, et al., "Human Endothelial Cells Express Integrin Receptors on the Luminal Aspect of Their Membrane," Blood 80(2):437-46, 1992.
Dillman, "Monoclonal Antibodies for Treating Cancer," Annals of Internal Medicine, 111(7) 592-600, 1989.
Farnoud, et al., "Fibronectin Isoforms Are Differentially Expressed in Normal and Adenomatous Human Anterior Pituitaries," Int. J. Cancer, 61:27-34, 1995.
Garin-Chesa, et al., "Cell Surface Glycoprotein of Reactive Stromal Fibroblasts As A Potential Antibody Target in Human Epithelial Cancers," Proc. Natl. Acad. Sci. USA, 87:7235-39, 1990.
Groenewegen, et al., "Lymphokine Dependence of In Vivo Expression of MHC Class II Antigens by Endothelium," Nature, 316:361-63, 1985.
Harris and Emery, "Therapeutic Antibodies--The Coming of Age," Btech, 11:42-44, 1993.
June, et al., "T-Cell Proliferation Involving the CD28 Pathway Is Associated with Cyclosporine-Resistant Interleukin 2 Gene Expression," Molecular and Cellular Biology 7(12):4473-81, 1987.
Kaczmarek, et al., "Distribution of Oncofetal Fibronectin Isoforms in Normal Hyperplastic and Neoplastic Human Breast Tissues," Int. J. Cancer, 58:11-16, 1994.
Koulova et al., "The CD28 Ligand B7/BB1 Provides Costimulatory Signal for

Alloactivation of CD4.sup.+ T Cells," J. Exp. Med. 173:759-62, 1991.
Kurosawa, et al., "Early Appearance and Activation of Natural Killer Cells in Tumor-Infiltrating Lymphoid Cells During Tumor Development," Eur. J. Immunol. 23:1029-33, 1993.
Lampugnani, et al., "The Role of Integrins in the Maintenance of Endothelial Monolayer Integrity," The Journal of Cell Biology, 112(3):479-90, 1991.
Linnala, et al., "Human Amnion Epithelial Cells Assemble Tenascins and Three Fibronectin Isoforms in the Extracellular Matrix," FEBS, 314(1,2):74-78, 1993.
Maeda, et al., "Production and Characterization of Tumor Infiltrating Lymphocyte Clones Derived from B16-F10 Murine Melanoma," The Journal of Investigative Dermatology 97(2):183-89, 1991.
Natali, et al., "Comparitive Analysis of the Expression of the Extracellular Matrix Protein Tenascin in Normal Human Fetal, Adult and Tumor Tissues," Int. J. Cancer, 47:811-16, 1991.
Oyama, et al., "Coordinate Oncodevelopmental Modulation of Alternative Splicing of Fibronectin Pre-Messenger RNA at ED-A, ED-B and CS1 Regions in Human Liver Tumors," Cancer Research 53:2005-11, 1993.
Peters, et al., "Expression of the Alternatively Spliced EIIIB Segment of Fibronectin," Cell Adhesion and Communication, 3:67-89, 1995.
Pober et al., "Ia Expression by Vascular Endothelium Is Inducible by Activated T Cells and by Human .gamma. Interferon," J. Exp. Med. 157: 1339-53, 1983.
Pohl, et al., "CD30-Antigen-Sepcific Targeting and Activation of T Cells via Murine Bispecific Monoclonal Antiodies Against CD3 and CD28: Potential Use for the Treatment of Hodgkin's Lymphoma," Int. J. Cancer, 54:820-27, 1993.
Renner, et al., "Cure of Xenografted Human Tumors by Bispecific Monoclonal Antibodies and Human T Cells," Science, 264:833-35, 1994.
Rettig, et al., "Cell-Surface Glycoproteins of Human Sarcomas: Differential Expression in Normal and Malignant Tissues and Cultured Cells," Proc. Natl. Acad. Sci. USA, 85:3110-14, 1988.
Rettig, et al., Identification of Endosialin, A Cell Surface Glycoprotein of Vascular Endothelial Cells in Human Cancer,Proc. Natl. Acad. Sci. USA, 89:10832-36, 1992.
Rosenberg, Steven, "Lymphokine-Activated Killer Cells: A New Approach to Immunotherapy of Cancer," JNCI 75(4):595-603, 1985.
Rosenberg, et al., "Observations of the Systemic Administration of Autologous Lymphokine-Activated Killer Cells and Recombinant Interleukin-2 to Patients with Metastatic Cancer," The New England Journal of Medicine, 313(23):1485-92, 1985.
Ruiter, et al., "Monoclonal Antibody-Defined Human Endothelial Antigens as Vascular Markers," J. Investigative Dermatol., 93(2):25S-32S, 1989.
Saiki et al., "Anti-metastatic and Anti-invasive Effects of Polymeric Arg-Gly-Asp (RGD) Peptide, Poly(RGD), and Its Analogues," Jpn. J. Cancer Res. 81:660-67, 1990.
Saiki et al., "Inhibition of Tumor Angiogenesis by a Synthetic Cell-Adhesive Polypeptide Containing the Arg-Gly-Asp (RGD) Sequence of Fibronectin, Poly(RGD)," Jpn. J. Cancer Res. 81:668-75, 1990.
Schlingemann, et al., "Differential Expression of Markers for Endothelial Cells, Pericytes, and Basal Lamina in the Microvasculature of Tumors and Granulation Tissue," Am. J. Pathol., 138(6):1335-47, 1991.
Schwarzbauer, "Alternative Splicing of Fibronectin: Three Variants, Three Functions," BioEssays 13(10)527-33, 1991.
Siri, et al., "Human Tenascin: Primary Structure, Pre-mRNA Splicing Patterns and Localization of the Epitopes Recognized by Two Monoclonal Antibodies," Nucleic Acids Research, 19(3):525-31, 1991.
Steiniger, et al., "Interferon-.gamma. in Vivo, Induction and Loss of Class II MHC Antigens and Immture Myelomonocytic Cells in Rat Organs," Eur. J. Immunol. 18:661-69, 1988.
Street, et al., "In Vivo Administration of Fab' Fragments of Anti-L3T4 (GK1.5) Antibody Inhibits the T Helper Cell Function of Murine Lymph Node Cells," Cellular Immunology 120:75-81, 1989.
Thompson, et al., "CD28 Activation Pathway Regulates the Production of Multiple T-Cell-Derived Lymphokines/Cytokines," Proc. Natl. Acad. Sci. USA, 86:1333-37, 1989.
Ueda, et al., "Selective Distribution of Fibronectin to a Tumor-Cell Line," Cancer Letters 31:261-65, 1986.
Vartio, et al., "Differential Expression of the ED Sequence-Containing Form of

Cellular Fibronectin in Embryonic and Adult Human Tissues," Journal of Cell Science, 88:419-30, 1987.
Welt, et al., "Phase I Localization Study of .sup.131 I-monoclonal Antibody F19 Detecting an Activation Antigen of Neoplastic Stroma," Proceedings of the American Association for Cancer Research, 33:319, 1992, Abstract No. 1900.
Werb, et al., "Signal Transduction through the Fibronectin Receptor Induces Collagenase and Stromelysin Gene Expression," The Journal of Cell Biology., 109:877-89, 1989.
Songsivilai & Lachmann, "Bispecific antibody: a tool for diagnosis and treatment of disease", Clin. exp. Immunol., 79, 315-321 (1990).
Dermer, "Another Anniversary for the War on Cancer", Bio/technology, 12, 320 (1994).
Pober and Cotran, "What Can Be Learned From the Expression of Endothelial Adhesion Molecules in Tissues?", Laboratory Investigation, 64(3), 301-305 (1991).
Vitetta et al., "Redesigning Nature's Poisons to Create Anti-Tumor Reagents," Science, 238:1098-1104, 1987.
Burgess et al., "Possible Dissociation of the Heparin-Binding and Mitogenic Activities of Heparin-Biding (Acidic Fibroblast) Growth Factor-1 from Its Receptor-Binding Activities by Site-Directed Mutagenesis of a Single Lysine Residue," J. Cell. Biol., 111:2129-2138, 1990.
Gillies and Wesolowski, "Antigen Binding and Biological Activities of Engineered Mutant Chimeric Antibodies with Human Tumor Specificities," Hum. Antibod. Hybridomas, 1(1);47-54, 1990.
Lapierre et al., "Three Distinct Classes of Regulatory Cytokines Contrl Endothelial Cell MHC Antigen Expression," J. Exp. Med., 167:794-804, 1988.
Lazar et al., "Transforming Growth Factor .alpha.: Mutation of Aspartic Acid 47 and Leucine 48 Results in Different Biological Activities," Mol. Cell Biol., 8(3):1247-1252, 1988.
Qian et al., "Human Peripheral Blood Lymphocytes Targeted with Bispecific Antibodies Release Cytokines That Are Essential for Inhibiting Tumor Growth," J. Immunol., 146(9):3250-3256, 1991.
Tao and Morrison, "Studies of Aglycosylated Chimeric Mouse-Human IgG--Role of Carbohydrate in the Structure and Effector Functions Mediated by the Human IgG Constant Region," J. Immunol., 143(8):2595-2601, 1989.
Waldman, Thomas A., "Monoclonal Antibodies in Diagnosis and Therapy," Science, 252: 1657-1662, 1991.
Wen et al., "Effects of .gamma.-Interferon on Major Histocompatibility Complex Antigen Expression and Lymphocytic Infiltration in the 9L Gliosarcoma Brain Tumor Model: Implications for Strategies of Immunotherapy," J. Neuroimmunol., 36:57-68, 1992.
Osborn et al., "Leukocyte Adhesion to Endothelium in Inflammation," Cell, 62:3-6, 1990.
June et al., "Role of the CD28 Receptor in T-Cell Activation," Immunology Today, 11(6):211-216, 1990.
Denekamp, "Vascuaalr Attack as a Therapeutic Strategy for Cancer," Cancer and Metastasis Reviews, 9:267-282, 1990.
Scott et al., "Anti-CD3 Antibody Induces Rapid Expression of Cytokine Genes In Vivo," The Journal of Immunology, 145(7):2183-2188, 1990.
O'Connell & Edidin, "A Mouse Lymphoid Endothelial Cell Line Immortalized by Simian Virus 40 Binds Lymphocytes and Retains Functional Characteristics of Normal Endothelial Cells," The Journal Immunology, 144(2):521-525, 1990.
Ledbetter et al., "CD 28 Ligation in T-Cell Activation: Evidence for Two Signal Transduction," Abstract only, Blood, 75(7):1531-1539, 1990.
Watanabe et al., "Exogenous Expression of Mouse Interferon .gamma. cDNA in Mouse Neuroblastoma C1300 Cells Results in Reduced Tumorigenicity by Augmented Anti-Tumor Immunity," Proceedings of the National Academy of Scientists, 86:9456-9460, 1989.
Schutt et al., "Human Monocyte Activation Induced by an Anti-CD14 Monoclonal Antibody," Immunology Letters, 19:321-328, 1988.
Thorpe et al., "Improved Antitumor Effects of Immunotoxins Prepared with Deglycosylated Ricin A-Chain and Hindered Disulfide Linkages," Cancer Research, 48:6396-6403, 1988.
Glennie et al., "Preparation and Performance of Bispecific (F)ab'.gamma.).sub.2 Antibody Containing Thioether-Linked Fab'.gamma. Fragments," The Journal of

Immunology, 139(7):2367-2375, 1987.
Bevilacqua et al., "Identification of an Inducible Endothelial-Leukocyte Adhesion Molecule," Proceedings of the National Academy of Scientists, 84:9238-9242, 1987.
Cotran et al., "Introduction and Detection of a Human Endothelial Activation Antigen In Vivo," Abstract only, The Journal of Experimental Medicine, 164(2):661-666, 1986.
Groenewegen et al., "Lymphokine Dependence of In Vivo Expression of MHC Class II Antigens by Endothelium," Nature, 316:361-263, 1985.
Moretta et al., Abstract only, The Journal of Experimental Medicine, 162(3):823-838, 1985.
Vaickus & Foon, "Overview of Monoclonal Antibodies in the Diagnosis and Therapy of Cancer," Cancer Investigation, 93(2):295-209, 1991.
Hagemeier et al., "A Monoclonal Antibody Reacting with Endothelial Cells of Budding Vessels in Tumors and Inflammatory Tissues, and Non-Reactive with Normal Adult Tissues," International Journal of Cancer, 38:481-488, 1986.
Duijvestijn et al., "Lymphoid Tisse- and Inflammation-Specific Endothelial Cell Differentiation defined by Monoclonal Antibodies," The Journal of Immunology, 138(3):713-719, 1987.
Murray et al., "Vascular Markers for Murine Tumours," Radiotherapy and Oncology, 16:221-234, 1989.
Schlingemann et al., "Monoclonal Antibody PAL-E Specific for Endothelium," Laboratory Investigation, 52(1):71-76, 1985.
Bruland et al., "New Monoclonal Antibodies Specific for Human Sarcomas," International Journal of Cancer, 38:27-31, 1986.
Reisfeld et al., "Human Tumor-Associated Antigens Defined by Monoclonal Antibodies," CRC Critical Reviews in Immunology, 5(1):27-53, 1984.
Schlom et al., "Monoclonal Antibodies Reactive with Breast Tumor-Associated Antigens," Advances in Cancer Research, 43:143-173, 1985.
Kaplan, "the Diagnostic and Therapeutic Use of Monoclonal Antibodies in Colorectal Cancer," Hematology/Oncology Clinics of North American, 3(1):125-134, 1989.
Smith & Teng, "Clinical Applications of Monoclonal Antibodies in Gynecologic Oncology," Cancer, 60:2068-2074, 1987.
Stavrou, "Monoclonal Antibodies in Neuro-Oncology," Neurosurgery Review, 13:7-18, 1990.
Shepard et al., "Monoclonal Antibody Therapy of Human Cancer: Taking the HEr2 Protooncogene to the Clinic," Journal of Clinical Immunology, 11(3):117-127, 1991.
Szymendera, "Clincal Usefulness of Three Monoclonal Antibody-Defined Tumour Markers: CA 19-9, CA 50, and CA 125," Tumor Biology, 7:333-342, 1986.
Catane & Longo, "Monoclonal Antibodies for Cancer Therapy," Israel Journal of Medical Sciences, 24:471-476, 1988.
Greiner et al., "Applications of Monoclonal Antibodies and Recombinant Cytokines for the Treatment of Human Colorectal and Other Carcinomas," Journal of Surgical Oncology Supplement, 2:9-13, 1991.
Thor & Edgerton, "Monoclonal Antibodies Reactive with Human Breast or Ovarian Carcinoma: In Vivo Applications," Seminars in Nuclear Medicine, 19(4):295-308, 1989.
Thorpe et al., "Selective Killing of Proliferating Vascular Endothelial Cells by an Anti-Fibronectin Immunotoxin," 16th LH Gray Conference, University of Manchester Institute of Science and Technology, Sep. 17-21, 1990.
Ghose, Tarun I. et al., "Preparation of Antibody-Linked Cytotoxic Agents," Methods in Enzymology, 93:280-333, 1983.
Knowles, Phillip P. and Thorpe, Philip E., "Purification of Immunotoxins Containing Ricin A-Chain and Abrin A-Chain Using Blue Sepharose CL-6B," Analytical Biochemistry, 160:440-443, 1987.
Wang, Theodore S.T. et al., "Photoreactive In-Cyclodextrin Inclusion Complex: a New Heterobifunctional Reagent for Antibody Labeling," Nuclear Medicine and Biology, 19(8):897-902, 1992.
Alvarez, J.A. et al., "Localization of Basic Fibroblast Growth Factor and Vascular Endothelial Growth Factor in Human Glial Neoplasms," Modern Pathology, 5(3):303-307, 1992.
Brown, Lawrence F. et al., "Expression of Vascular Permeability Factor (Vascular Endothelial Growth Factor) and Its Receptors in Adenocarcinomas of the

Gastrointestinal Tract," Cancer Research, 53:4727-4735, 1993.
Kim, K. Jin et al., "Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumor growth in vivo," Nature, 362:841-843, 1993.
Dvorak, Harold F. et al., "Distribution of Vascular Permeability Factor (Vascular Endothelial Growth Factor) in Tumors: Concentration in Tumor Blood Vessels," J. Exp. Med., 174:1275-1278, 1991.
Gerlach, Herwig et al., "Enhanced Responsiveness of Endothelium in the Growing/Motile State to Tumor Necrosis Factor/Cachectin," J. Exp. Med., 170:913-931, 1989.
Gougos, Anne et al., "Identification of distinct epitopes of endoglin, an RGD-containing glycoprotein of endothelial cells, leukemic cells, and syncytiotrophoblasts," International Immunology, 4(1):83-92, 1991.
Gougos, Anne et al., "Identification of a Human Endothelial Cell Antigen with Monoclonal Antibody 44G4 Produced Against a Pre-B Leukemic Cell Line," The Journal of Immunology, 141:1925-1933, 1988.
Gougos, Anne et al., "Biochemical Characterization of the 44G4 Antigen from the Hoon Pre-B Leukemic Cell Line," The Journal of Immunology, 141:1934-1940, 1988.
Jakeman, Lyn B. et al., "Binding Sites for Vascular Endothelial Growth Factor Are Localized on Endothelial Cells in Adult Rat Tissues," J. Clin. Invest., 89:244-253, 1992.
Nabel, Elizabeth G. et al., "Recombinant fibroblast growth factor-1 promotes intimal hyperplasia and angiogensis in arteries in vivo," Nature, 362:844, 1993.

O'Connell, P.J. et al., "Endoglin: a 180-kD endothelial cell and macrophage restricted differentiation molecule," Clin. Exp. Immunol., 90:154-159, 1992.
Plate, K.H. et al., "Up-Regulation of Vascular Endothelial Growth Factor and Its Cognate Receptors in a Rat Glioma Model of Tumor Angiogenesis," Cancer Research, 53(23):5822-5827, 1993.
Plate, Karl H. et al., "Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo," Nature, 359:845-848, 1992.
Rettig, Wolfgang J. et al., "Identification of endosialin, a cell surface glycoprotein of vascular endothelial cells in human cancer," Proc. Natl. Acad. Sci. USA, 89:10832-10836, 1992.
Sarma, Vidya et al., "Cloning of a Novel Tumor Necrosis Factor-.alpha.-Inducible Primary Response Gene that is Differentially Expressed in Development and Capillary Tube-Like Formation in vitro," The Journal of Immunology, 148:3302-3312, 1992.
Senger, Donald R. et al., "Vascular permeability factor (VPF, VEGF) in tumor biology," Cancer and Metatasts Reviews, 12:303-324, 1993.
Shweiki, Dorit et al., "Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis," Nature, 359:843-845, 1992.
Wang, J.M. et al., "A Monoclonal Antibody Detects Heterogeneity in Vascular Endothelium of Tumours and Normal Tissues," Int. J. Cancer, 54:363-370, 1993.
Westphal, Johan R. et al., "A New 180-kDa Dermal Endothelial Cell Activation Antigen: In Vitro and In Situ Characteristics," The Journal of Investigative Dermatology, 100(1):27-34, 1993.
Yeo, Kiang-Teck et al., "Vascular Permeability Factor (Vascular Endothelial Growth Factor) in Guinea Pig and Human Tumor and Inflammatory Effusions," Cancer Research, 53:2912-2918, 1993.
Thorpe et al., "Targeting to Proliferating Vascular Endothelium," Int. Symp. on Angio., abstracts, Mar., 1991.

ART-UNIT: 166
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ABSTRACT:

The present invention relates generally to methods and compositions for targeting the vasculature of solid tumors using immunologically-based reagents. In particular aspects, antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature of solid tumor masses through recognition of tumor vasculature-associated antigens, such as, for example, through endoglin binding, or through the specific induction of endothelial cell surface antigens on

vascular endothelial cells in solid tumors.

26 Claims, 19 Drawing figures

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U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
Re33405	October 1990	Chu et al.	N/A
4172124	October 1979	Koprowski et al.	N/A
4331647	May 1982	Goldenberg	N/A
4446122	May 1984	Chu et al.	N/A
4554101	November 1985	Hopp	N/A
4690890	September 1987	Loor et al.	N/A
5019384	May 1991	Gefter et al.	N/A
5055404	October 1991	Ueda et al.	N/A
5153118	October 1992	Wright, Jr. et al.	N/A
5221605	June 1993	Bard et al.	N/A
5238808	August 1993	Bard et al.	N/A
5273743	December 1993	Ahlem et al.	N/A
5310687	May 1994	Bard et al.	N/A

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 81/01849	July 1981	WOX	
WO 95/03334	February 1995	WOX	
WO 95/30758	November 1995	WOX	

OTHER PUBLICATIONS

Christensson, Eur J. Biochem 220:45 1994.
Alfthan and Stenman, "Falsely Low Results Obtained with the Hybritech Tandem.RTM.-R PSA Assay," Clinical Chemistry, 34(10):2152, 1988.
Ball et al., "Detailed Mapping of the Antigenicity of the Surface Unit Glycoprotein of Equine Infectious Anemia Virus by Using Synthetic Peptide Strategies," Journal of Virology, 66(2):732-742, Feb., 1992.
Bonci et al., "Characterization of immunoreactive octapeptides of human-cytomegalovirus gp58," Eur. J. Biochem., 215:383-387, 1993.
Bridon and Dowell, "Structural Comparison of Prostate-Specific Antigen and Human Glandular Kallikrein Using Molecular Modeling," Urology, 45(5): 801-806, May, 1995.
Bruccoleri et al., "Structure of antibody hypervariable loops reproduced by a conformational search algorithm," Nature, 335:564-568, Oct., 1988.
Carlacci and Englander, "The Loop Problem in Proteins: A Monte Carlo Simulated Annealing Approach," Biopolymers, 33:1271-1286, 1993.
Chan et al., "Prostate-Specific Antigen as a Marker for Prostatic Cancer: a Monoclonal and a Polyclonal Immunoassay Compared," Clin. Chem., 33(10):1916-1920, 1987.
Chou and Fasman, "Empirical Predictions of Protein Conformation," Ann. Rev. Biochem., 47:251-276, 1978.
Chou and Fasman, "Prediction of Protein Conformation," Biochemistry, 13(2):222-245, 1974.
Chu et al., "Prostate-Specific Antigenic Domain of Human Prostate Specific Antigen Identified with Monoclonal Antibodies," The Journal of Urology, 141:152-156, Jan., 1989.
Corr et al., "Endogenous Peptides of a Soluble Major Histocompatibility Complex Class I Molecule, H-2L.sup.d.sub.s : Sequence Motif, Quantitative Binding, and Molecular Modeling of the Complex," The Journal of Experimental Medicine, 176:1681-1692, Dec., 1992.
Corr et al., "H-2D.sup.d Exploits a Four Residue Peptide Binding Motif," The Journal of Experimental Medicine, 178:1877-1892, Dec., 1993.
Das and Lindstrom, "Epitope Mapping of Antibodies to Acetylcholine Receptor .alpha. Subunits Using Peptides Synthesized on Polypropylene Pegs," Biochemistry, 30:2470-2477, 1991.
Dernick et al., "Detection of Prostate Specific Antigen (PSA) with Monoclonal Antibodies Detected Against Native and Denatured PSA," In: Journal of Cellular Biochemistry (Abstract), Keystone Symposia on Molecular and Cellular Biology, Suppl. 16D, p. 96, Mar., 1992.
Dill et al., "Cooperativity in protein-folding kinetics," Proc. Natl. Acad. Sci. USA, 90:1942-1946, Mar., 1993.
Dyson et al., "The immunodominant site of a synthetic immunogen has a conformational preference in water for a type-II reverse turn," Nature, 318:480-483, Dec., 1985.
Fasman et al., "Conformational Analysis of the Immunodominant Epitopes of the Curcumsporozoite Protein of Plasmodium Falciparum and knowlesi," Biopolymers, 29:123-130, 1990.
Fetrow and Bryant, "New Programs for Protein Tertiary Structure Prediction," Bio/Technology, 11:479-484, Apr., 1993.
Fine et al., "Predicting Antibody Hypervariable Loop Conformations II: Minimization and Molecular Dynamics Studies of MCPC603 From Many Randomly Generated Loop Conformations," Proteins: Structure, Function, and Genetics, 1:342-362, 1986.
Graves et al., "Comparison of a Polyclonal and Monoclonal Immunoassay for PSA: Need for An International Antigen Standard," The Journal of Urology, 144:1516-1522, Dec., 1990.
Groneborn and Clore, "Experimental Support for the `Hydrophobic Zipper` Hypothesis," Science, 263:536, Jan., 1994.

Henttu and Vihko, "cDNA Coding for the Entire Human Prostate Specific Antigen Shows High Homologies to the Human Tissue Kallikrein Genes," Biochemical and Biophysical Research Communications, 160(2):903-910, Apr., 1989.
Hodges et al., "Antigen-Antibody Interaction," The Journal of Biological Chemistry, 263(24):11768-11775, Aug., 1988.
Hofmann et al., "Protein-Water Interaction Energies as Predictor for Antigenic Determinants," Molecular Immunology, 27(10):1057-1060, 1990.
Hohne et al., "Structural Base of the Interaction of a Monoclonal Antibody Against p24 of HIV-1 with its Peptide Epitope," Molecular Immunology, 30(13):1213-1221, 1993.
Holzmann et al., "Assessment of the antigenic structure of tick-borne encephalitis virus by the use of synthetic peptides," Journal of General Virology, 74:2031-2035, 1993.
Jameson and Wolf, "The antigenic index: a novel algorithm for predicting antigenic determinants," CABIOS, 4(1):181-186, 1988.
Janin, "Surface and inside volumes in globular proteins," Nature, 277:491-492, Feb., 1979.
Javaherian et al., "Principal neutralizing domain of the human immunodeficiency virus type 1 envelope protein," Proc. Natl. Acad. Sci. USA, 86:6768-6772, Sep., 1989.
Jurincic-Winkler et al., "Clinical Evaluation of a New Prostate-Specific Antigen Sandwich ELISA Which Employs Four Monoclonal Antibodies Directed at Different Epitopes of Prostate-Specific Antigen," Eur. Urol., 24:487-491, 1993.
Kessler, "Use of Protein A-Bearing Staphylococci for the Immunoprecipitation and Isolation of Antigens from Cells," Methods in Enzymology, 73:442-459, 1981.
Kolaskar and Tongaonkar, "A semi-empirical method for prediction of antigenic determinants on protein antigens," FEBS, 276(1,2):172-174, Dec., 1990.
Kyte and Doolittle, "A Simple Method for Displaying the Hydropathic Character of Protein," J. Mol. Biol., 157:105-132, 1982.
McCormack et al., "Molecular Forms of Prostate-Specific Antigen and the Human Kallikrein Gene Family: A New Era," Urology, 45(5):729-744, May, 1995.
Meek, "Prediction of peptide retention times in high-pressure liquid chromatography on the basis of amino acid composition," Proc. Natl. Acad. Sci. USA, 77(3):1632-1636, Mar., 1980.
Pellequer et al., "Correlation between the location of antigenic sites and the prediction of turns in proteins," Immunology Letters, 36:83-100, 1993.
Pellequer et al., "Predicting Location of Continuous Epitopes in Proteins from Their Primary Structures," Methods in Enyzmology, 203:176-197, 1991.
Ralston et al., "Synthetic Peptides Used To Locate the .alpha.-Bungarotoxin Binding Site and Immunogenic Regions on .alpha. Subunits of the Nicotinic Acetylcholine Receptor," Biochemistry, 26:3261-3266, 1987.
Reddehase et al., "A pentapeptide as minimal antigenic determinant for MHC class I-restricted T lymphocytes," Nature, 337:651-653, Feb., 1989.
Regenmortel, "Synthetic Peptides and Monoclonal Antibodies in Immunoassays," Nucl. Med. Biol., 14(4):277-280, 1987.
Regenmortel, "Structural and functional approaches to the study of protein antigenicity," Immunology Today, 10(8):266-272, 1989.
Rock et al., "Evaluation of a Monoclonal Immunoradiometric Assay for Prostate-Specific Antigen," Clinical Chemistry, 33(12):2257-2261, 1987.
Rothbard and Taylor, "A sequence pattern common to T cell epitopes," The EMBO Journal, 7(1):93-100, 1988.
Scott et al., "Mapping the Locations of the Epitopes of Five Monoclonal Antibodies to the Core Protein of Dermatan Sulfate Proteoglycan II (Decorin)," The Journal of Biological Chemistry, 268(16):11558-11564, Jun., 1993.
Silverio et al., "New Ultrasensitive Assay Development by Using Monoclonal Antibodies for Detecting Prostate-Specific Antigen," Eur. Urol., 21(supp. 1):79-82, 1992.
Snijders et al., "Identification of linear epitopes on Semliki Forest virus E2 membrane protein and their effectiveness as a synthetic peptide vaccine," Journal of General Virology, 72:557-565, 1991.
Suhrbier et al., "Prediction of an HLA B8-restricted influenza epitope by motif," Immunology, 79:171-173, May, 1993.
Thole et al., "A Major Immunogenic 36,000-Molecular-Weight Antigen from Mycobacterium leprae Contains an Immunoreactive Region of Proline-Rich Repeats," Infection and Immunity, 58(1):80-87, Jan., 1990.

Turkes et al., "Prostate-specific Antigen: Protein in Analysis," J. Eur. J. Cancer, 27(5):650-652, 1991.
Vessella and Lange, "Issues in the Assessment of PSA Immunoassays," Urologic Clinics of North America, 20(4):607-619, Nov., 1993.
Wolf et al., "An integrated family of amino acid sequence anaylsis programs," CABIOS, 4(1):187-191, 1988.
Wright, Jr. et al., "Generation and Characterization of Monoclonal Antibodies to Prostate Secretory Protein," Int. J. Cancer, 46:39-49, 1990.
Zhou et al., "Multiple Forms of Prostate-Specific Antigen in Serum: Differences in Immunorecognition by Monoclonal and Polyclonal Assays," Clin. Chem., 39(12):2483-2491, 1993.
Martin-Moe et al., "Hydrophobic Interactions and the Design of Receptor Mimetic Peptides," Peptide Research, 8(2):70-76, 1995.
Takayama et al., "A Brief Review of Ultrasensitive Prostate-Specific Antigen Assays for the Evaluation of Patients After Radical Prostatectomy," World J. Urol., 11:192-195, 1993.
Zvi et al., "The Principal Neutralizing Determinant of HIV-1 Located in V3 of gp120 Forms a 12-Residue Lop by Internal Hydrophobic Interactions," FEBS Letters, 368:267-270, 1995.
Ausubel et al., Current Protocols in Molecular Biology, vol. 2, publ. Greene Publishing Associates and Wiley-Interscience, 11.14.1-11.15.4, 1989.
Bander, "Current Status of Monoclonal Antibodies for Imaging and Therapy of Prostate Cancer"; Seminars in Oncology, 21:5, 607-612, 1994.
Leroy et al., "Radioimmunodetection of Lymph Node Invasion in Prostatic Cancer", Cancer, 64:1-5, 1989.
Lundwall et al., "Molecular Cloning of Human Prostate Specific Antigen cDNA", FEBS Letters, 214:2, 317-322, 1987.
Palfreyman,et al., "Guidelines for the Production of Polypeptide Specific Antisera Using Small Synthetic Oligopeptides as Immunogens", Journal of Immunological Methods, 75:383-393, 1984.
Sela, "Synthetic Approaches to Applied Medical Aspects of Immunology", Asian Journal of Infectious Diseases, 1:97-103, 1977.

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PRIMARY-EXAMINER: Scheiner; Toni R.
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ABSTRACT:

Peptides derived from prostate specific antigen (PSA) that correspond to the immunodominant epitopes found in the native antigen are disclosed. These peptides were identified using a method that predicts continuous, immunodominant epitopes. Anti-PSA antibodies, methods for their production and their use in diagnostic assays also are disclosed.

10 Claims, 1 Drawing figures

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TITLE: Methods for targeting the vasculature of solid tumors

DATE-ISSUED: July 7, 1998

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APPL-NO: 8/ 456495
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PARENT-CASE:
The present application is a division of copending application Ser. No. 08/350,212, filed Dec. 5, 1994, which is a continuation-in-part of co-pending U.S. patent application Ser. No. 08/205,330, filed Mar. 2, 1994; which is a continuation-in-part of U.S. patent application Ser. No. 07/846,349, filed Mar. 05, 1992, now abandoned. The entire text and figures of which disclosures are specifically incorporated by reference herein without disclaimer.

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US-CL-CURRENT: 424/1.49; 424/138.1, 424/143.1, 424/145.1, 424/178.1, 424/179.1, 424/181.1, 424/183.1, 424/93.21, 530/387.2, 530/388.2, 530/388.73, 530/391.7
FIELD-OF-SEARCH: 424/1.49, 424/1.69, 424/138.1, 424/143.1, 424/145.1, 424/179.1, 424/181.1, 424/183.1, 424/178.1, 424/93.21, 530/387.2, 530/387.3, 530/388.22, 530/388.73, 530/389.1, 530/391.7, 530/391.9

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U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4456550	June 1984	Dvorak et al.	260/112R
4472509	September 1984	Gansow et al.	N/A
4536387	August 1985	Sakamoto et al.	424/14
5021236	June 1991	Gries et al.	N/A
5081034	January 1992	Bevilacqua et al.	N/A
5342757	August 1994	Garin-Chesa et al.	435/7.21
5399346	March 1995	Anderson et al.	424/93.21
5403713	April 1995	Bevilacqua et al.	435/7.1
5632991	May 1997	Gimbrone, Jr.	424/178.1

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
9003801	April 1990	WOX	
WO 90/13300	November 1990	WOX	
WO 90/12585	November 1990	WOX	
WO 92/12729	August 1992	WOX	
WO 92/19646	November 1992	WOX	
WO 93/08210	April 1993	WOX	
WO 93/08473	April 1993	WOX	
WO 94/11499	May 1994	WOX	
WO 94/10202	May 1994	WOX	

OTHER PUBLICATIONS

Aoyagi, "Distribution of Plasma Fibronectin in the Metastatic Lesion of Cancer: Experimental Study by Autoradiography," Thrombosis Research, 49:265-75, 1988 Without Month.
Balza et al., "Production and Characterization of Monoclonal Antibodies Specific for Different Epitopes of Human Tenascin," FEBS 332(1,2):39-43, 1993 Without Month.
Bjorndahl, et al., "Human T Cell Activation: Differential Response to Anti-CD28 As Compared to Anti-CD3 Monoclonal Antibodies," Eur. J. Immunol., 19:881-87, 1989 Without Month.
Blanchard, et al., "Infiltration of Interleukin-2-Inducible Killer Cells in Ascitic Fluid and Pleural Effusions of Advanced Cancer Patients," Cancer Research, 48:6321-27, 1988 Without Month.
Bohlen, et al., "Cytolysis of Leukemic B-Cells by T-Cells Activated via Two Bispecific Antibodies," Cancer Research, 53:4310-14, 1993 Without Month.
Borsi, et al., "Expression of Different Tenascin Isoforms in Normal, Hyperplastic and Neoplastic Human Breast Tissues," Int. J. Cancer, 52:688-92, 1992 Without Month.
Boyer, et al., "Differential Induction by Interferons of Major Histocompatibility Complex-Encoded and Non-Major Histocompatibility Complex-Encoded Antigens in Human Breast and Ovarian Carcinoma Cell Lines," Cancer Research, 49:2928-34, 1989 Without Month.
Burton-Wurster, et al., "Expression of the Ed B Fibronectin Isoform in Adult Human Articular Cartilage," Biochemical and Biophysical Research Communication 165(2): 782-87, 1989 w/o Month.
Collins, et al., "Immune Interferon Activates Multiple Class II Major Histocompatibility Complex Genes and the Associated Invariant Chain Gene in Human Endothelial Cells and Dermal Fibroblasts," Proc. Natl. Acad. Sci. USA, 81:4917-21, 1984 w/o Month.
Carnemolla et al., "A Tumor-associated Fibronectin Isoform Generated by Alternative Splicing of Messenger RNA Precursors," The Journal of Cell Biology, 108:1139-48, 1989 w/o Month.
Carnemolla et al., "The Inclusion of the Type III Repeat ED-B in the Fibronectin Molecule Generates Conformational Modifications that Unmask a Cryptic Sequence," The Journal of Biological Chemistry, 267(34):24589:92, 1992 w/o Month.
Carnemolla, et al., "Phage Antibodies with Pan-Species Recognition of the Oncofoetal Angiogenesis Marker Fibronectin ED-B Domain," Int. J. Cancer 68:397-405, 1996 w/o Month.
Castellani, et al., "The Fibronectin Isoform Containing the ED-B Oncofoetal Domain: A Marker of Angiogenesis," Int. J. Cancer, 59:612-18, 1994 w/o Month.
Conforti, et al., "Human Endothelial Cells Express Integrin Receptors on the Luminal Aspect of Their Membrane," Blood 80(2):437-46, 1992 w/o Month.
Dillman, "Monoclonal Antibodies for Treating Cancer," Annals of Internal Medicine, 111(7) 592-600, 1989 w/o Month.
Farnoud, et al., "Fibronectin Isoforms Are Differentially Expressed in Normal and Adenomatous Human Anterior Pituitaries," Int. J. Cancer, 61:27-34, 1995 w/o Month.
Garin-Chesa, et al., "Cell Surface Glycoprotein of Reactive Stromal Fibroblasts As A Potential Antibody Target in Human Epithelial Cancers," Proc. Natl. Acad. Sci. USA, 87:7235-39, 1990 w/o Month.

Groenewegen, et al., "Lymphokine Dependence of In Vivo Expression of MHC Class II Antigens by Endothelium," Nature, 316:361-63, 1985 w/o Month.
Harris and Emery, "Therapeutic Antibodies--The Coming of Age," Btech, 11:42-44, 1993 w/o Month.
June, et al., "T-Cell Proliferation Involving the CD28 Pathway Is Associated with Cyclosporine-Resistant Interleukin 2 Gene Expression," Molecular and Cellular Biology 7(12):4473-81, 1987 w/o Month.
Kaczmarek, et al., "Distribution of Oncofetal Fibronectin Isoforms in Normal Hyperplastic and Neoplastic Human Breast Tissues," Int. J. Cancer, 58:11-16, 1994 w/o Month.
Koulova et al., "The CD28 Ligand B7/BB1 Provides Costimulatory Signal for Alloactivation of CD4.sup.+ T Cells," J. Exp. Med. 173:759-62, 1991 w/o Month.
Kurosawa, et al., "Early Appearance and Activation of Natural Killer Cells in Tumor-Infiltrating Lymphoid Cells During Tumor Development," Eur. J. Immunol. 23:1029-33, 1993 w/o Month.
Lampugnani, et al., "The Role of Integrins in the Maintenance of Endothelial Monolayer Integrity," The Journal of Cell Biology, 112(3):479-90, 1991 w/o Month.
Linnala, et al., "Human Amnion Epithelial Cells Assemble Tenascins and Three Fibronectin Isoforms in the Extracellular Matrix," FEBS, 314(1,2):74-78, 1993 w/o Month.
Maeda, et al., "Production and Characterization of Tumor Infiltrating Lymphocyte Clones Derived from B16-F10 Murine Melanoma," The Journal of Investigative Dermatology 97(2):183-89, 1991 w/o Month.
Natali, et al., "Comparative Analysis of the Expression of the Extracellular Matrix Protein Tenascin in Normal Human Fetal, Adult and Tumor Tissues," Int. J. Cancer, 47:811-16, 1991 w/o Month.
Oyama, et al., "Coordinate Oncodevelopmental Modulation of Alternative Splicing of Fibronectin Pre-Messenger RNA at ED-A, ED-B and CS1 Regions in Human Liver Tumors," Cancer Research 53:2005-11, 1993 w/o Month.
Peters, et al., "Expression of the Alternatively Spliced EIIIB Segment of Fibronectin," Cell Adhesion and Communication, 3:67-89, 1995 w/o Month.
Pober et al., "Ia Expression by Vascular Endothelium Is Indcuible by Activated T Cells and by Human .gamma. Interferon," J. Exp Med. 157: 1339-53, 1983 w/o Month.
Pohl, et al., "CD30-Antigen-Specific Targeting and Activation of T Cells via Murine Bispecific Monoclonal Antibodies Against CD3 and CD28: Potential Use for the Treatment of Hodgkin's Lymphoma," Int. J. Cancer, 54:820-27, 1993 w/o Month.

Renner, et al., "Cure of Xenografted Human Tumors by Bispecific Monoclonal Antibodies and Human T Cells," Science, 264:833-35, 1994 w/o Month.
Rettig, et al., "Cell-Surface Glycoproteins of Human Sarcomas: Differential Expression in Normal and Malignant Tissues and Cultured Cells," Proc. Natl. Acad. Sci. USA, 85:3110-14, 1988 w/o Month.
Rettig, et al., Identification of Endosialin, A Cell Surface Glycoprotein of Vascular Endothelial Cells in Human Cancer, Proc. Natl. Acad. Sci. USA, 89:10832-36, 1992 w/o Month.
Rosenberg, Steven, "Lymphokine-Activated Killer Cells: A New Approach to Immunotherapy of Cancer," JNCI 75(4):595-603, 1985 w/o Month.
Rosenberg, et al., "Observations of the Systemic Administration of Autologous Lymphokine-Activated Killer Cells and Recombinant Interleukin-2 to Patients with Metastatic Cancer," The New England Journal of Medicine, 313(23):1485-92, 1985 w/o Month.
Ruiter, et al., "Monoclonal Antibody-Defined Human Endothelial Antigens as Vascular Markers," J. Investigative Dermatol., 93(2):25S-32S, 1989 w/o Month.
Saiki et al., "Anti-metastatic and Anti-invasive Effects of Polymeric Arg-Gly-Asp (RGD) Peptide, Poly(RGD), and Its Analogues," Jpn. J. Cancer Res. 81:660-67, 1990 w/o Month.
Saiki et al., "Inhibition of Tumor Angiogenesis by a Synthetic Cell-Adhesive Polypeptide Containing the Arg-Gly-Asp (RGD) Sequence of Fibronectin, Poly(RGD)," Jpn. J. Cancer Res. 81:668-75, 1990 w/o Month.
Schlingemann, et al., "Differential Expression of Markers for Endothelial Cells, Pericytes, and Basal Lamina in the Microvasculature of Tumors and Granulation Tissue," Am. J. Pathol. 138(6):1335-47, 1991 w/o Month.
Schwarzbauer, "Alternative Splicing of Fibronectin: Three Variants, Three

Functions," BioEssays 13(10)527-33, 1991 w/o Month.
Siri, et al., "Human Tenascin: Primary Structure, Pre-mRNA Splicing Patterns and Localization of the Epitopes Recognized by Two Monoclonal Antibodies," Nucleic Acids Research, 19(3):525-31, 1991 w/o Month.
Steiniger, et al., "Interferon-.gamma. in Vivo. Induction and Loss of Class II MHC Antigens and Immture Myelomonocytic Cells in Rat Organs," Eur. J. Immunol. 18:661-69, 1988 w/o Month.
Street, et al., "In Vivo Administration of Fab' Fragments of Anti-L3T4 (GK1.5) Antibody Inhibits the T Helper Cell Function of Murine Lymph Node Cells," Cell Immunology 120:75-81, 1989 w/o Month.
Thompson, et al., "CD28 Activation Pathway Regulates the Production of Multiple T-Cell-Derived Lymphokines/Cytokines," Proc. Natl. Acad. Sci. USA, 86:1333-37, 1989 w/o Month.
Ueda, et al., "Selective Distribution of Fibronectin to a Tumor-Cell Line," Cancer Letters 31:261-65, 1986 w/o Month.
Vartio, et al., "Differential Expression of the ED Sequence-Containing Form of Cellular Fibronectin in Embryonic and Adult Human Tissues," Journal of Cell Science, 88:419-30, 1987 w/o Month.
Welt, et al., "Phase I Localization Study of .sup.131 I-monoclonal Antibody F19 Detecting an Activation Antigen of Neoplastic Stroma," Proceedings of the American Association for Cancer Research, 33:319, 1992 w/o Month, Abstract No. 1900.
Werb, et al., "Signal Transduction through the Fibronectin Receptor Induces Collagenase and Stromelysin Gene Expression," The Journal of Cell Biology., 109:877-89, 1989 w/o Month.
Songsivilai & Lachmann, "Bispecific antibody: a tool for diagnosis and treatment of disease", Clin. exp. Immunol.,. 79, 315-321 (1990) w/o Month.
Dermer, "Another Anniversary for the War on Cancer", Bio/technology, 12, 320 (1994) w/o Month.
Pober and Cotran, "What Can Be Learned From the Expression of Endothelial Adhesion Molecules in Tissues?", Laboratory Investigation, 64(3), 301-305 (1991) w/o Month.
Vitetta et al., "Redesigning Nature's Poisons to Create Anti-Tumor Reagents," Science, 238:1098-1104, 1987 w/o Month.
Burgess et al., "Possible Dissociation of the Heparin-Binding and Mitogenic Activities of Heparin-Binding (Acidic Fibroblast) Growth Factor-1 from Its Receptor-Biding Activities by Site-Directed Mutagenesis of a Single Lysine Residue," J. Cell Biol., 111:2129-2138, 1990 w/o Month.
Gillies and Wesolowski, "Antigen Binding and Biological Activities of Engineered Mutant Chimeric Antibodies with Human Tumor Specificities," Hum. Antibod. Hybridomas, 1(1):47-54, 1990 w/o Month.
Lapierre et al. , "Three Distinct Classes of Regulatory Cytokines Control Endothelial Cell MHC Antigen Expression," J. Exp. Med., 167:794-804, 1988 w/o Month.
Lazar et al. , "Transforming Growth Factor .alpha.: Mutation of Aspartic Acid 47 and Leucine 48 Results in Different Biological Activities," Mol. Cell Biol., 8(3):1247-1252, 1988 w/o Month.
Tao and Morrison, "Studies of Aglycosylated Chimeric Mouse-Human IgG--Role of Carbohydrate in the Structure and Effector Functions Mediated by the Human IgG Constant Region," J. Immunol., 143(8):2595-2601, 1989 w/o Month.
Waldman, Thomas A., "Monoclonal Antibodies in Diagnosis and Therapy," Science, 252: 1657-1662, 1991 w/o Month.
Wen et al. , "Effects of .gamma.-Interferon on Major Histocompatibility Complex Antigen Expression and Lymphocytic Infiltration in the 9L Gliosarcoma Brain Tumor Model: Implications for Strategies of Immunotherapy," J. Neuroimmunol., 36:57-68, 1992 w/o Month.
Burrows and Thorpe, "Targeting the Vasculature of Solid Tumors," Journal of Controlled Release, 28:195-202, Jan. 1994.
Thorpe and Burrows, "Antibody-Directed Targeting of the Vasculature of Solid Tumors," Breast Cancer Research and Treatment, 36(2):237-251, 1995 w/o Month.
Osborn et al., "Leukocyte Adhesion to Endothelium in Inflammation," Cell, 62:3-6, 1990 w/o Month.
June et al., "Role of the CD28 Receptor in T-Cell Activation," Immunology Today, 11(6):211-216, 1990 w/o Month.
Denekamp, "Vascular Attack as a Therapeutic Strategy for Cancer," Cancer and

Metastasis Reviews, 9:267-282, 1990 w/o Month.
Scott et al., "Anti-CD3 Antibody Induces Rapid Expression of Cytokine Genes In Vivo," The Journal of Immunology, 145(7):2183-2188, 1990 w/o Month.
O'Connell & Edidin, "A Mouse Lymphoid Endothelial Cell Line Immortalized by Simian Virus 40 Binds Lymphocytes and Retains Functional Characteristics of Normal Endothelial Cells," The Journal of Immunology, 144(2):521-525, 1990 w/o Publ. Month.
Ledbetter et al., "CD 28 Ligation in T-Cell Activation: Evidence for Two Signal Transduction," Abstract only, Blood, 75(7):1531-1539, 1990 w/o Publ. Month.
Watanabe et al., "Exogenous Expression of Mouse Interferon .gamma. cDNA in Mouse Neuroblastoma C1300 Cells Results in Reduced Tumorigenicity by Augmented Anti-Tumor Immunity," Proceedings of the National Academy of Scientists, 86:9456-9460, 1989 w/o Publ. Month.
Schutt et al., "Human Monocyte Activation Induced by an Anti-CD14 Monoclonal Antibody," Immunology Letters, 19:321-328, 1988 w/o Publ. Month.
Thorpe et al., "Improved Antitumor Effects of Immunotoxins Prepared with Deglycosylated Ricin A-Chain and Hindered Disulfide Linkages," Cancer Research, 48:6396-6403, 1988 w/o Publ. Month.
Glennie et al., "Preparation and Performance of Bispecific (F(ab'.gamma.).sub.2 Antibody Containing Thioether-Linked Fab'.gamma. Fragments," The Journal of Immunology, 139(7):2367-2375, 1987 w/o Publ. Month.
Bevilacqua et al., "Identification of an Inducible Endothelial-Leukocyte Adhesion Molecule," Proceedings of the National Academy of Scientists, 84:9238-9242, 1987 w/o Publ. Month.
Cotran et al., "Induction and Detection of a Human Endothelial Activation Antigen In Vivo," Abstract only, The Journal of Experimental Medicine, 164(2):661-666, 1986 w/o Publ. Month.
Groenewegen et al., "Lymphokine Dependence of In Vivo Expression of MHC Class II Antigens by Endothelium," Nature, 316:361-263, 1985 w/o Publ. Month.
Moretta et al., Abstract only, The Journal of Experimental Medicine, 162(3):823-838, 1985 w/o Publ. Month.
Vaickus & Foon, "Overview of Monoclonal Antibodies in the Diagnosis and Therapy of Cancer," Cancer Investigation, 93(2):295-209, 1991 w/o Publ. Month.
Hagemeier et al., "A Monoclonal Antibody Reacting with Endothelial Cells of Budding Vessels in Tumors and Inflammatory Tissues, and Non-Reactive with Normal Adult Tissues," International Journal of Cancer, 38:481-488, 1986 w/o Publ. Month.
Duijvestijn et al., "Lymphoid Tissue- and Inflammation-Specific Endothelial Cell Differentiation defined by Monoclonal Antibodies," The Journal of Immunology, 138(3):713-719, 1987 w/o Publ. Month.
Murray et al., "Vascular Markers for Murine Tumours," Radiotherapy and Oncology, 16:221-234, 1989 w/o Publ. Month.
Schlingemann et al., "Monoclonal Antibody PAL-E Specific for Endothelium," Laboratory Investigation, 52(1):71-76, 1985 w/o Publ. Month.
Bruland et al., "New Monoclonal Antibodies Specific for Human Sarcomas," International Journal of Cancer, 38:27-31, 1986 w/o Publ. Month.
Reisfeld et al., "Human Tumor-Associated Antigens Defined by Monoclonal Antibodies," CRC Critical Reviews in Immunology, 5(1):27-53, 1984 w/o Publ. Month.
Schlom et al., "Monoclonal Antibodies Reactive with Breast Tumor-Associated Antigens," Advances in Cancer Research, 43:143-173, 1985 w/o Publ. Month.
Kaplan, "The Diagnostic and Therapeutic Use of Monoclonal Antibodies in Colorectal Cancer," Hematology/Oncology Clinics of North American, 3(1):125-134, 1989 w/o Publ. Month.
Smith & Teng, "Clinical Applications of Monoclonal Antibodies in Gynecologic Oncology," Cancer, 60:2068-2074, 1987 w/o Month.
Stavrou, "Monoclonal Antibodies in Neuro-Oncology," Neurosurgery Review, 13:7-18, 1990 w/o Month.
Shepard et al., "Monoclonal Antibody Therapy of Human Cancer: Taking the HEr2 Protooncogene to the Clinic," Journal of Clinical Immunology, 11(3):117-127, 1991 w/o Month.
Szymendera, "Clinical Usefulness of Three Monoclonal Antibody-Defined Tumor Markers: CA 19-9, CA 50, and CA 125," Tumour Biology, 7:333-342, 1986 w/o Month.

Catane & Longo, "Monoclonal Antibodies for Cancer Therapy," Israel Journal of

Medical Sciences, 24:471-476, 1988 w/o Month.
Greiner et al., "Applications of Monoclonal Antibodies and Recombinant Cytokines for the Treatment of Human Colorectal and Other Carcinomas," Journal of Surgical Oncology Supplement, 2:9-13, 1991 w/o Month.
Thor & Edgerton, "Monoclonal Antibodies Reactive with Human Breast or Ovarian Carcinoma: In Vivo Applications," Seminars in Nuclear Medicine, 19(4):295-308, 1989 w/o Month.
Thorpe et al., "Selective Killing of Proliferating Vascular Endothelial Cells by an Anti-Fibronectin Receptor Immunotoxin," 16th LH Gray Conference, University of Manchester Institute of Science and Technology, Sep. 17-21, 1990.
Thorpe et al., "Targeting To Proliferating Vascular Endothelium," International Symposium on Angiogenesis, St. Gallen, Switzerland, Abstract, Mar. 13-15, 1991.
Ghose, Tarun I. et al., "Preparation of Antibody-Linked Cytotoxic Agents," Methods in Enzymology, 93:280-333, 1983 w/o Month.
Knowles, Philip P. and Thorpe, Philip E., "Purification of Immunotoxins Containing Ricin A-Chain and Abrin A-Chain Using Blue Sepharose CL-6B," Analytical Biochemistry, 160:440-443, 1987 w/o Publ. Month.
Wang, Theodore S.T. et al., "Photoreactive In-Cyclodextrin Inclusion Complex: a New Heterobifunctional Reagent for Antibody Labeling," Nuclear Medicine and Biology, 19(8):897-902, 1992 w/o Publ. Month.
Alvarez, J.A. et al., "Localization of Basic Fibroblast Growth Factor and Vascular Endothelial Growth Factor in Human Glial Neoplasms," Modern Pathology, 5(3):303-307, 1992 w/o Publ. Month.
Brown, Lawrence F. et al., "Expression of Vascular Permeability Factor (Vascular Endothelial Growth Factor) and Its Receptors in Adenocarcinomas of the Gastrointestinal Tract," Cancer Research, 53:4727-4735, 1993 w/o Publ. Month.
Kim, K. Jin et al., "Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumor growth in vivo," Nature, 362:841-843, 1993 w/o Publ. Month.
Dvorak, Harold F. et al., "Distribution of Vascular Permeability Factor (Vascular Endothelial Growth Factor) in Tumors: Concentration in Tumor Blood Vessels," J. Exp. Med., 174:1275-1278, 1991 w/o Publ. Month.
Gerlach, Herwig et al., "Enhanced Responsiveness of Endothelium in the Growing/Motile State to Tumor Necrosis Factor/Cachectin," J. Exp. Med., 170:913-931, 1989 w/o Publ. Month.
Gougos, Anne et al., "Identification of distinct epitopes of endoglin, an RGD-containing glycoprotein of endothelial cells, leukemic cells, and syncytiotrophoblasts," International Immunology, 4(1):83-92, 1991 w/o Publ. Month.
Gougos, Anne et al., "Identification of a Human Endothelial Cell Antigen with Monoclonal Antibody 44G4 Produced Against a Pre-B Leukemic Cell Line," The Journal of Immunology, 141:1925-1933, 1988 w/o Publ. Month.
Gougos, Anne et al., "Biochemical Characterization of the 44G4 Antigen from the Hoon Pre-B Leukemic Cell Line," The Journal of Immunology, 141:1934-1940, 1988 w/o Publ. Month.
Jakeman, Lyn B. et al., "Binding Sites for Vascular Endothelial Growth Factor Are Localized on Endothelial Cells in Adult Rat Tissues," J. Clin. Invest., 89:244-253, 1992 w/o Publ. Month.
Nabel, Elizabeth, G. et al., "Recombinant fibroblast growth factor-1 promotes intimal hyperplasia and angiogenesis in arteries in vivo," Nature, 362:844, 1993 w/o Publ. Month.
O'Connoll, P.J. et al., "Endoglin: a 180-kD endothelial cell and macrophage restricted differentiation molecule," Clin. Exp. Immunol., 90:154-159, 1992 w/o Publ. Month.
Plate, K.H. et al., "Up-Regulation of Vascular Endothelial Growth Factor and Its Cognate Receptors in a Rat Glioma Model of Tumor Angiogenesis," Cancer Research, 53(23):5822-5827, 1993 w/o Publ. Month.
Plate, Karl H. et al., "Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo," Nature, 359:845-848, 1992 w/o Publ. Month.
Rettig, Wolfgang J. et al., "Identification of endosialin, a cell surface glycoprotein of vascular endothelial cells in human cancer," Proc. Natl. Acad. Sci. USA, 89:10832-10836, 1992 w/o Publ. Month.
Sarma, Vidya et al., "Cloning of a Novel Tumor Necrosis Factor-.alpha.-Inducible Primary Response Gene that is Differentially Expressed in Development and

Capillary Tube-Like Formation in vitro," The Journal of Immunology, 148:3302-3312, 1992.
Senger, Donald R. et al., "Vascular permeability factor (VPF, VEGF) in tumor biology," Cancer and Metatasts Reviews, 12:303-324, 1993 w/o Publ. Month.
Shweiki, Dorit et al., "Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis," Nature, 359:843-845, 1992 w/o Publ. Month.
Wang, J.M. et al., "A Monoclonal Antibody Detects Heterogeneity in Vascular Endothelium of Tumours and Normal Tissues," Int. J. Cancer, 54:363-370, 1993 w/o Publ. Month.
Westphal, Johan R. et al., "A New 180-kDa Dermal Endothelial Cell Activation Antigen: In Vitro and In Situ Characteristics," The Journal of Investigative Dermatology, 100(1):27-34, 1993 w/o Publ. Month.
Yeo, Kiang-Teck et al., "Vascular Permeability Factor (Vascular Endothelial Growth Factor) in Guinea Pig and Human Tumor and Inflammatory Effusions," Cancer Research, 53:2912-2918, 1993 w/o Publ. Month.
Buring et al., "Endoglin is expressed on a subpopulation of immature erythroid cells of normal human bone marrow," Leukemia, 5(10):841-847, 1991 w/o Month.
Dvorak et al., "Structure of Solid Tumors and Their Vasculature: Implications for Therapy with Monoclonal Antibodies," Cancer Cells, 3(3):77-85, 1991 w/o Month.
Gougos & Letarte, "Primary Structure of Endoglin, an RGD-containing Glycoprotein of Human Endothelial Cells," The Journal of Biological Chemistry, 265(15):8361-8364, 1990 w/o Month.
Qian, et al., "Human PBL Targeted with Bi-specific Antibodies Release Cytokines that are Essential for Inhibiting Tumor Growth", Jour. of Immunology, vol. 146, No. 9, pp. 3250-3256, 1991.

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ABSTRACT:

The present invention relates generally to methods and compositions for targeting the vasculature of solid tumors using immunological- and growth factor-based reagents. In particular aspects, antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature of solid tumor masses through recognition of tumor vasculature-associated antigens, such as, for example, through endoglin binding, or through the specific induction of endothelial cell surface antigens on vascular endothelial cells in solid tumors.

23 Claims, 27 Drawing figures

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U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
4456550	June 1984	Dvorak et al.	N/A
4472509	September 1984	Gansow et al.	N/A
5021236	June 1991	Gries et al.	N/A
5081034	January 1992	Bevilacqua et al.	N/A

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO81/01145	April 1981	WOX	
WO90/13300	November 1990	WOX	
WO90/12585	November 1990	WOX	
WO92/12729	August 1992	WOX	
WO92/19646	November 1992	WOX	
WO93/08210	April 1993	WOX	
WO93/08473	April 1993	WOX	
WO93/17715	September 1993	WOX	
WO94/05328	March 1994	WOX	
WO94/11499	May 1994	WOX	
WO94/10202	May 1994	WOX	

OTHER PUBLICATIONS

Burrows et al., "A Murine Model for Antibody-Directed Targeting of Vascular Endothelial Cells in Solid Tumors," Cancer Research, 52:5954-5962, Nov. 1992.
Burrows and Thorpe, "Targeting the Vasculature of Solid Tumors," Journal of Controlled Release, 28:195-202, Jan. 1994.
Clauss et al., "A Polypeptide Factor Produced by Fibrosarcoma Cells That Induces Endothelial Tissue Factor and Enhances the Procoagulant Response to Tumor Necrosis Factor/Cachetin," The Journal of Biological Chemistry, 265(12):7078-7083, Apr. 1990.
Thorpe and Burrows, "Antibody-Directed Targeting of the Vasculature of Solid Tumors," Breast Cancer Research and Treatment, 36(2):237-251, 1995.
Yamazaki et al., "Bispecific Monoclonal Antibodies with Specificities for Activated Platelets and Thrombolytic Agents, Their Production and Use," Abstract for Canadian Patent Application CA 2039259; Chem Abstracts, 117(11), Abstract #109988.
Osborn et al., "Leukocyte Adhesion to Endothelium in Inflammation," Cell, 62:3-6, 1990.
June et al., "Role of the CD28 Receptor in T-Cell Activation," Immunology Today, 11(6):211-216, 1990.
Denekamp, "Vascular Attack as a Therapeutic Strategy for Cancer," Cancer and Metastasis Reviews, 9:267-282, 1990.
Scott et al., "Anti-CD3 Antibody Induces Rapid Expression of Cytokine Genes In Vivo," The Journal of Immunology, 145(7):2183-2188, 1990.
O'Connell & Edidin, "A Mouse Lymphoid Endothelial Cell Line Immortalized by Simian Virus 40 Binds Lymphocytes and Retains Functional Characteristics of Normal Endothelial Cells," The Journal of Immunology, 144(2):521-525, 1990.
Ledbetter et al., "CD 28 Ligation in T-Cell Activation: Evidence for Two Signal Transduction," Abstract only, Blood, 75(7):1531-1539, 1990.
Watanabe et al., "Exogenous Expression of Mouse Interferon .gamma. cDNA in Mouse Neuroblastoma C1300 Cells Results in Reduced Tumorigenicity by Augmented Anti-Tumor Immunity," Proceedings of the National Academy of Scientists, 86:9456-9460, 1989.
Schutt et al., "Human Monocyte Activation Induced by an Anti-CD14 Monoclonal Antibody," Immunology Letters, 19:321-328, 1988.
Thorpe et al., "Improved Antitumor Effects of Immunotoxins Prepared with Deglycosylated Ricin A-Chain and Hindered Disulfide Linkages," Cancer Research, 48:6396-6403, 1988.
Glennie et al., "Preparation and Performance of Bispecific (F(ab'.gamma.).sub.2 Antibody Containing Thioether-Linked Fab'.gamma. Fragments," The Journal of Immunology, 139(7):2367-2375, 1987.
Bevilacqua, et al., "Identification of an Inducible Endothelial-Leukocyte Adhesion Molecule," Proceedings of the National Academy of Scientists, 84:9238-9242, 1987.
Cotran et al., "Induction and Detection of a Human Endothelial Activation Antigen In Vivo," Abstract only, The Journal of Experimental Medicine, 164(2):661-666, 1986.

Groenewegen et al., "Lymphokine Dependence of In Vivo Expression of MHC Class II Antigens by Endothelium," Nature, 316:361-263, 1985.
Moretta et al., Abstract only, The Journal of Experimental Medicine, 162(3):823-838, 1985.
Vaickus & Foon, "Overview of Monoclonal Antibodies in the Diagnosis and Therapy of Cancer," Cancer Investigation, 93(2):295-209, 1991.
Hagemeier et al., "A Monoclonal Antibody Reacting with Endothelial Cells of Budding Vessels in Tumors and Inflammatory Tissues, and Non-Reactive with Normal Adult Tissues," International Journal of Cancer, 38:481-488, 1986.
Duijvestijn et al., "Lymphoid Tissue-and Inflammation-Specific Endothelial Cell Differentiation defined by Monoclonal Antibodies," The Journal of Immunology, 138(3):713-719, 1987.
Murray et al., "Vascular Markers for Murine Tumours," Radiotherapy and Oncology, 16:221-234, 1989.
Schlingemann et al., "Monoclonal Antibody PAL-E Specific for Endothelium," Laboratory Investigation, 52(1):71-76, 1985.
Bruland et al., "New Monoclonal Antibodies Specific for Human Sarcomas," International Journal of Cancer, 38:27-31, 1986.
Reisfeld et al., "Human Tumor-Associated Antigens Defined by Monoclonal Antibodies," CRC Critical Reviews in Immunology, 5(1):27-53, 1984.
Schlom et al., "Monoclonal Antibodies Reactive with Breast Tumor-Associated Antigens," Advances in Cancer Research, 43:143-173, 1985.
Kaplan, "The Diagnostic and Therapeutic Use of Monoclonal Antibodies in Colorectal Cancer," Hematology/Oncology Clinics of North American, 3(1):125-134, 1989.
Smith & Teng, "Clinical Applications of Monoclonal Antibodies in Gynecologic Oncology," Cancer, 60:2068-2074, 1987.
Stavrou, "Monoclonal Antibodies in Neuro-Oncology," Neurosurgery Review, 13:7-18, 1990.
Shepard et al., "Monoclonal Antibody Therapy of Human Cancer: Taking the HEr2 Protooncogene to the Clinic," Journal of Clinical Immunology, 11(3):117-127, 1991.
Szymendera, "Clinical Usefulness of Three Monoclonal Antibody-Defined Tumor Markers: CA 19-9, CA 50, and CA 125," Tumour Biology, 7:333-342, 1986.
Catane & Longo, "Monoclonal Antibodies for Cancer Therapy," Israel Jorunal of Medical Sciences, 24:471-476, 1988.
Greiner et al., "Applications of Monoclonal Antibodies and Recombinant Cytokines for the Treatment of Human Colorectal and Other Carcinomas," Journal of Surgical Oncology Supplement, 2:9-13, 1991.
Thor & Edgerton, "Monoclonal Antibodies Reactive with Human Breast or Ovarian Carcinoma: In Vivo Applications," Seminars in Nuclear Medicine, 19(4):295-308, 1989.
Thorpe et al., "Selective Killing of Proliferating Vascular Endothelial Cells by an Anti-Fibronectin Receptor Immunotoxin," 16th LH Gray Conference, University of Manchester Institute of Science and Technology, Sep. 17-21, 1990.
Thorpe et al., "Targeting To Proliferating Vascular Endothelium," International Symposium on Angiogenesis, St. Gallen, Switzerland, Abstract, Mar. 13-15, 1991.
Ghose, Tarun I. et al., "Preparation of Antibody-Linked Cytotoxic Agents," Methods in Enzymology, 93:280-333, 1983.
Knowles, Phillip P. and Thorpe, Philip E., "Purification of Immunotoxins Containing Ricin A-Chain and Abrin-A-Chain Using Blue Sepharose CL-6B," Analytical Biochemistry, 160:440-443, 1987.
Wang, Theodore S.T. et al., "Photoreactive In-Cyclodextrin Inclusion Complex: a New Heterobifunctional Reagent for Antibody Labeling," Nuclear Medicine and Biology, 19(8):897-902, 1992.
PCT Search Report mailed Jun. 25, 1993.
Alvarez, J.A. et al., "Localization of Basic Fibroblast Growth Factor and Vascular Endothelial Growth Factor in Human Glial Neoplasms," Modern Pathology, 5(3):303-307, 1992.
Brown, Lawrence F. et al., "Expression of Vascular Permeability Factor (Vascular Endothelial Growth Factor) and Its Receptors in Adenocarcinomas of the Gastrointestinal Tract," Cancer Research, 53:4727-4735, 1993.
Kim, K. Jin et al., "Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumor growth in vivo," Nature, 362:841-843, 1993.
Dvorak, Harold F. et al., "Distribution of Vascular Permeability Factor

(Vascular Endothelial Growth Factor) in Tumors: Concentration in Tumor Blood Vessels," J. Exp. Med., 174:1275-1278, 1991.
Gerlach, Herwig et al., "Enhanced Responsiveness of Endothelium in the Growing/Motile State to Tumor Necrosis Factor/Cachetin," J. Exp. Med., 170:913-931, 1989.
Gougos, Anne et al., "Identification of distinct epitopes of endoglin, an RGD-containing glycoprotein of endothelial cells, leukemic cells, and synctiotrophoblasts," International Immunology, 4(1):83-92, 1991.
Gougos, Anne et al., "Identification of a Human Endothelial Cell Antigen with Monoclonal Antibody 44G4 Produced Against a Pre-B Leukemic Cell Line," The Journal of Immunology, 141:1925-1933, 1988.
Gougos, Anne et al., "Biochemical Characterization of the 44G4 Antigen from the Hoon Pre-B Leukemic Cell Line," The Journal of Immunology, 141:1934-1940, 1988.
Jakeman, Lyn B. et al., "Binding Sites for Vascular Endothelial Growth Factor Are Localized on Endothelial Cells in Adult Rat Tissues," J. Clin. Invest., 89:244-253, 1992.
Nabel, Elizabeth G. et al., "Recombinant fibroblast growth factor-1 promotes intimal hyperplasia and angiogenesis in arteries in vivo," Nature, 362:844, 1993.
O'Connell, P.J. et al., "Endoglin: a 180-kD endothelial cell and macrophage restricted differentiation molecule," Clin. Exp. Immunol., 90:154-159, 1992.
Plate, K.H. et al., "Up-Regulation of Vascular Endothelial Growth Factor and Its Cognate Receptors in a Rat Glioma Model of Tumor Angiogenesis," Cancer Research, 53(23):5822-5827, 1993.
Plate, Karl H. et al., "Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo," Nature, 359:845-848, 1992.
Rettig, Wolfgang J. et al., "Identification of endosialin, a cell surface glycoprotein of vascular endothelial cells in human cancer," Proc. Natl. Acad. Sci. USA, 89:10832-10836, 1992.
Sarma, Vidya et al., "Cloning of a Novel Tumor Necrosis Factor-.alpha.-Inducible Primary Response Gene that is Differentially Expressed in Development and Capillary Tube-Like Formation in vitro," The Journal of Immunology, 148:3302-3312, 1992.
Senger, Donald R. et al., "Vascular permeability factor (VPF, VEGF) in tumor biology," Cancer and Metatasts Reviews, 12:303-324, 1993.
Shweiki, Dorit et al., "Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis," Nature, 359:843-845, 1992.
Wang, J.M. et al., "A Monoclonal Antibody Detects Heterogeneity in Vascular Endothelium of Tumours and Normal Tissues," Int. J. Cancer, 54:363-370, 1993.
Westphal, Johan R. et al., "A New 180-kDa Dermal Endothelial Cell Activation Antigen: In Vitro and In Situ Characteristics," The Journal of Investigative Dermatology, 100(1):27-34, 1993.
Yeo, Kiang-Teck et al., "Vascular Permeability Factor (Vascular Endothelial Growth Factor) in Guinea Pig and Human Tumor and Inflammatory Effusions," Cancer Research, 53:2912-2918, 1993.
Buring et al., "Endoglin is expressed on a subpopulation of immature erythroid cells of normal human bone marrow," Leukemia, 5(10):841-847, 1991.
Dvorak et al., "Structure of Solid Tumors and Their Vasclature: Implications for Therapy with Monoclonal Antibodies," Cancer Cells, 3(3):77-85, 1991.
Gougos & Letarte, "Primary Structure of Endoglin, an RGD-containing Glycoprotein of Human Endothelial Cells," The Journal of Biological Chemistry, 265(15):8361-8364, 1990.
UTSD:344; U.S. Serial No. 08/295,868, Nationalization of PCT/US/01956; U.S. Filing date Sep. 6, 1994.
UTSD:393; U.S. Serial No. 08/205,330; filed Mar. 2, 1994.
UTSD:430; U.S. Serial No. 08/350,212; filed Dec. 5, 1994.
UTSD:451; U.S. Serial No. 08/456,495, filed Jun. 1, 1995; Divisional of UTSD:430.
UTSD:452; U.S. Serial No. 08/457,487, filed Jun. 1, 1995; Divisional of UTSD:430.
UTSD:454; U.S. Serial No. 08/457,031, filed Jun. 1, 1995; Divisional of UTSD:430.
UTSD:455; U.S. Serial No. 08/457,869, filed Jun. 1, 1995; Divisional of UTSD:430.

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ABSTRACT:

Disclosed are antibodies that specifically bind to endoglin. Conjugates of the antibodies linked to diagnostic or therapeutic agents are also provided. Methods of using the antibodies and conjugates are also disclosed, including methods of targeting the vasculature of solid tumors through recognition of the tumor vasculature-associated antigen, endoglin.

30 Claims, 37 Drawing figures

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